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The neural control of micturition

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Abstract

Micturition, or urination, occurs involuntarily in infants and young children until the age of 3 to 5 years, after which it is regulated voluntarily. The neural circuitry that controls this process is complex and highly distributed: it involves pathways at many levels of the brain, the spinal cord and the peripheral nervous system and is mediated by multiple neurotransmitters. Diseases or injuries of the nervous system in adults can cause the re-emergence of involuntary or reflex micturition, leading to urinary incontinence. This is a major health problem, especially in those with neurological impairment. Here we review the neural control of micturition and how disruption of this control leads to abnormal storage and release of urine.

The storage and periodic elimination of urine depend on the coordinated activity of smooth and striated muscles in the two functional units of the lower urinary tract, namely a reservoir (the urinary bladder) and an outlet consisting of the bladder neck, the urethra and the urethral sphincter[1,2]. The coordination between these organs is mediated by a complex neural control system that is located in the brain, the spinal cord and the peripheral ganglia.

The lower urinary tract differs from other visceral structures in several ways. First, its dependence on CNS control distinguishes it from structures that maintain a level of function even after the extrinsic neural input has been eliminated. It is also unusual in its pattern of activity and in the organization of its neural control mechanisms. For example, the bladder has only two modes of operation: storage and elimination. Thus, many of the neural circuits that are involved in bladder control have switch-like or phasic patterns of activity, unlike the tonic patterns that are characteristic of the autonomic pathways that regulate cardiovascular organs. In addition, micturition is under voluntary control and depends on learned behaviour that develops during maturation of the nervous system, whereas many other visceral functions are regulated involuntarily.

Owing to the complexity of the neural mechanisms that regulate bladder control, the process is sensitive to various injuries and diseases. This Review summarizes the results of recent studies in animals and humans that have provided new insights into the sensory and motor mechanisms that underlie voluntary and reflex micturition, the changes in neural pathways that occur following disease or injury that alters lower-urinary-tract function, and new therapies for the treatment of neurogenic bladder dysfunction.

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Peripheral innervation of the urinary tract

The requirement for voluntary control over the lower urinary tract necessitates complex interactions between autonomic (mediated by sympathetic and parasympathetic nerves) and somatic (mediated by pudendal nerves) efferent pathways[1,2] (FIG. 1a). The sympathetic innervation arises in the thoracolumbar outflow of the spinal cord, whereas the parasympathetic and somatic innervation originates in the sacral segments of the spinal cord. Afferent axons from the lower urinary tract also travel in these nerves.

Sympathetic postganglionic nerves — for example, the hypogastric nerve — release noradrenaline, which activates β-adrenergic inhibitory receptors in the detrusor muscle to relax the bladder, α-adrenergic excitatory receptors in the urethra and the bladder neck, and α- and β-adrenergic receptors in bladder ganglia[3,4] (FIG. 1b).

Parasympathetic postganglionic nerves release both cholinergic (acetylcholine, ACh) and non-adrenergic, non-cholinergic transmitters. Cholinergic transmission is the major excitatory mechanism in the human bladder[4] (FIG. 1b). It results in detrusor contraction and consequent urinary flow and is mediated principally by the M_3 muscarinic receptor, although bladder smooth muscle also expresses M_2 receptors[5]. Muscarinic receptors are also present on parasympathetic nerve terminals at the neuromuscular junction and in the parasympathetic ganglia[3,6]. Activation of these receptors on the nerve terminals can enhance (through M_1 receptors) or suppress (through M_4 receptors) transmitter release, depending on the intensity of the neural firing. Non-cholinergic excitatory transmission is mediated by ATP actions on P2X purinergic receptors in the detrusor muscle[7]. Inhibitory input to the urethral smooth muscle is mediated by nitric oxide (NO) that is released by parasympathetic nerves[4].

Somatic cholinergic motor nerves that supply the striated muscles of the external urethral sphincter arise in S2–S4 motor neurons in Onuf's nucleus and reach the periphery through the pudendal nerves[1,2] (FIG. 1a). A medially placed motor nucleus at the same spinal level supplies axons that innervate the pelvic floor musculature.

Sensations of bladder fullness are conveyed to the spinal cord by the pelvic and hypogastric nerves[1,8], whereas sensory input from the bladder neck and the urethra is carried in the pudendal and hypogastric nerves. The afferent components of these nerves consist of myelinated (Aδ) and unmyelinated (C) axons. The Aδ-fibres respond to passive distension and active contraction[8] and thus convey information about bladder filling. The C-fibres are insensitive to bladder filling under physiological conditions (they are therefore termed ‘silent’ C-fibres) and respond primarily to noxious stimuli such as chemical irritation[9] or cooling[10]. The cell bodies of Aδ-fibres and C-fibres are located in the dorsal root ganglia (DRG) at the level of S2–S4 and T11–L2 spinal segments. The axons synapse with interneurons that are involved in spinal reflexes and with spinal-tract neurons that project to higher brain centres that are involved in bladder control (see below).

A dense nexus of sensory nerves has been identified in the suburothelial layer of the urinary bladder in both humans and animals[11,12], with some terminal fibres projecting into the urothelium[13,14]. This suburothelial plexus is particularly prominent at the bladder neck but is relatively sparse at the dome of the bladder[15] and is thought to be critical in the sensory function of the urothelium.

The sensory role of non-neuronal cells

Animal studies have shown that non-neuronal cells also play a part in bladder sensory mechanisms. Traditionally viewed as merely a passive barrier, the urothelium is now known to have specialized sensory and signalling properties that allow it to respond to chemical and

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mechanical stimuli and to engage in reciprocal chemical communication with nerves in the bladder wall[1,16,17]. These properties include the expression of nicotinic, muscarinic, tachykinin, adrenergic, bradykinin and transient-receptor-potential vanilloid receptors (such as TRPV1)[18]; responsiveness to transmitters released from afferent nerves; a close physical association with afferent nerves; and the ability to release chemical mediators such as ATP[19], ACh and NO, which can regulate the activity of adjacent nerves and thereby trigger local vascular changes and/or reflex bladder contractions (FIG. 2).

The presence of muscarinic and nicotinic receptors in the urothelium[20–24] has focused attention on the role of ACh as a chemical mediator of neural–urothelial interactions. ACh is released from the urothelium in response to chemical or mechanical stimuli[16,25–27]. Application of a muscarinic receptor agonist to strips of rat bladder tissue induces membrane-potential transients and Ca^{2+} transients that begin near the urothelial–suburothelial interface and then spread to the detrusor smooth muscle, raising the possibility that the urothelium could regulate the generation of spontaneous, non-voiding contractions in the bladder[28]. Indeed, *in vivo* intravesical administration of muscarinic or nicotinic receptor agonists or anticholinesterase agents that increase the levels of endogenous ACh facilitates reflex bladder activity in rats and cats[26]. Thus, the clinical effect of antimuscarinic agents in overactive bladder (a decrease in sensory symptoms) might be related to the blocking of muscarinic receptors in the urothelium or in afferent nerves[16,26,29].

Stimulation of cholinergic receptors in the urothelium induces the release of ATP and an as yet unidentified smooth-muscle relaxant factor[20,23,26]. The function of ATP release from the urothelium has attracted considerable attention because intravesical administration of ATP induces detrusor overactivity by stimulating the purinergic receptor P2X ligand-gated ion channel 3 ($P2X_3$) or $P2X_{2/3}$ on afferent nerves[1,30]. Mice that lack $P2X_3$ receptors exhibit reduced bladder activity and inefficient voiding, suggesting that activation of $P2X_3$ receptors on bladder afferent nerves by ATP released from the urothelium is essential for normal bladder function[31].

The discovery of a suburothelial layer of myofibroblasts (also referred to as interstitial cells[32]) that lie in close proximity to nerves and are extensively linked by gap junctions[33] led to the proposal that these cells, together with afferent nerves, the urothelium and smooth muscle, might collectively have the properties to act as a stretch-receptor organ[33]. Furthermore, the demonstration that they express ATP-gated purinergic P2Y receptors[34] raises the possibility that they might respond to urothelial ATP release.

CNS pathways involved in micturition

The regulation of micturition requires connections between many areas in the brain and extensive tracts in the spinal cord that involve sympathetic, parasympathetic and somatic systems. Parasympathetic and sympathetic preganglionic neurons (PGNs) are located in the intermediate grey matter (laminae V–VII; FIG. 3) of spinal cord sacral and lumbar segments, respectively. Parasympathetic PGNs send dendrites into the dorsal commissure and into the lateral funiculus and lateral dorsal horn of the spinal cord[35] and exhibit an extensive axon collateral system that is distributed bilaterally in the cord[36]. A similar axon collateral system has not been identified in sympathetic preganglionic neurons. The somatic motor neurons that innervate the external urethral sphincter are located in the ventral horn (lamina IX) in Onuf's nucleus, have a similar arrangement of transverse dendrites and have an extensive system of longitudinal dendrites that travel within Onuf's nucleus[1,37].

Interneurons in the lumbosacral spinal cord of the rat that are involved in lower-urinary-tract function are located in the dorsal commissure, the superficial dorsal horn and the parasympathetic nucleus[38–41] (FIG. 3c). Some of these interneurons send long projections to

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the brain[41], whereas others make local connections in the spinal cord and participate in segmental spinal reflexes[42].

Afferent nerves from the bladder project to regions of the spinal cord that contain interneurons and parasympathetic PGN dendrites[43,44] (FIG. 3). Pudendal afferent pathways from the urethra and the urethral sphincter exhibit a similar pattern of termination[45,46]. The overlap between bladder and urethral afferents in the lateral dorsal horn and the dorsal commissure indicates that these regions are probably important sites of viscerosomatic integration that might be involved in coordinating bladder and sphincter activity.

In the brain, many neuron populations are involved in the control of the bladder, the urethra and the urethral sphincter. Some, such as the serotonergic neurons of the medullary raphe nuclei, the noradrenergic neurons of the locus coeruleus and the noradrenergic A5 cell group in the brain stem, are non-specific 'level-setting' mechanisms with diffuse spinal projections[47]. Others are specific for micturition: these include the neurons of Barrington's nucleus (also called the pontine micturition centre (PMC)) and those of the periaqueductal grey (PAG), cell groups in the caudal and preoptic hypothalamus, and the neurons of several parts of the cerebral cortex, in particular the medial frontal cortex[39,48] (FIG. 4).

There are interconnections between some of these brain areas and also between the brain and the lumbosacral spinal cord. Interneurons in the spinal cord project to the PAG[49] and (in rats) to the PMC (FIG. 4). Neurons in the PMC receive input from the PAG and from the anterior and caudal hypothalamus, but few or no other inputs; in turn, they send descending axons back to the parasympathetic nucleus in the spinal cord. The paraventricular nucleus of the hypothalamus projects non-specifically to all autonomic preganglionic motor neurons in the spinal cord, including the sacral parasympathetic and sphincter motor nuclei[50], but neurons in the lateral pons project rather selectively to the sphincter motor nucleus[50,51]. Thus, the supraspinal regulation of lower-urinary-tract function probably depends on multiple pathways carrying information between the brain and the spinal cord. The pathways that are specific for micturition[47] are the topic of this Review.

Regulation of bladder filling and voiding

The neural pathways that control lower-urinary-tract function are organized as simple on–off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet. Storage reflexes are activated during bladder filling and are organized primarily in the spinal cord, whereas voiding is mediated by reflex mechanisms that are organized in the brain (FIG. 5).

Bladder filling and the guarding reflex

Throughout bladder filling, the parasympathetic innervation of the detrusor is inhibited and the smooth and striated parts of the urethral sphincter are activated, preventing involuntary bladder emptying. This process is organized by urethral reflexes known collectively as the 'guarding reflex'. They are activated by bladder afferent activity that is conveyed through the pelvic nerves, and are organized by interneuronal circuitry in the spinal cord[52,53] (FIG. 5a). Some input from the lateral pons, which is also known as the 'L-region' or the 'pontine storage centre', might facilitate sphincter reflexes or have a role in involuntary sphincter control[51, 54]. In animals, reflex activation of the lumbar sympathetic pathway is involved in the inhibition of bladder smooth muscle[21], contraction of the bladder outlet and inhibition of parasympathetic activity at the level of the autonomic ganglia[31]. The importance of the sympathetic control in humans is less obvious, as sympatholytic drugs or resection of the sympathetic chain have little effect on bladder storage.

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In cats, afferent input from the bladder [41,50,55,56] ascends, through spinal interneurons in the lateral funiculus, to a relay station in the central PAG that in turn, through the lateral PAG, provides an excitatory input to the PMC[50] (FIG. 6). The presumed interconnection between the central and lateral PAG implies that signal processing occurs in the PAG, probably enabling higher centres to control the excitatory input to the PMC. In rats, ascending projections from the spinal cord also terminate directly in the PMC[57]. Additional bladder sensory input to the brain is carried by the spinothalamic tract, the spinohypothalamic tract and dorsal-column pathways to the nucleus gracilis.

Pharmacological and electrophysiological studies have indicated that the circuitry that feeds bladder afferent activity to midbrain and pontine centres and transmits efferent signals from the pons to the sacral cord (FIG. 5b) allows the spinobulbospinal voiding-reflex pathway to function as a switch that is either in a completely ‘off’ mode (storage) or a maximally ‘on’ mode (voiding)[52]. During bladder filling the parasympathetic efferent pathway to the bladder, including a population of PMC neurons, is turned off [58,59], but at a critical level of bladder distension the afferent activity arising from tension receptors in the bladder switches the pathway to maximal activity[58,60,61]. Drugs injected into the PMC can change the set-point (that is, the bladder volume) for activation of the switch without altering the magnitude of the voiding reflex[62]. Similarly, lesions in brain areas that lie rostral to the pons (for example, the diencephalon and the cerebral cortex) can alter the set-point of the voiding reflex, indicating that the switching circuit is tonically modulated by inhibitory and excitatory influences from the forebrain.

Operating in this way, the reflex circuitry shown in FIG. 5 would lead to involuntary bladder emptying (that is, incontinence) whenever the bladder volume reached a critical level. However, in continent individuals the firing of the voiding reflex is under strict voluntary control, enabling one to plan to void at a socially acceptable time and place. The decision to void, which is a crucial aspect of human behaviour, is based on a combination of factors, including one's emotional state, an appreciation of the social environment and the sensory signals arising from the bladder. Knowledge of the extent to which one's bladder content is comfortable and ‘safe’ is central in this process. Thus, voluntary control of the bladder and the urethra has two important aspects, namely registration of bladder filling sensations and manipulation of the firing of the voiding reflex. The PAG has a pivotal role in both[49]. On the one hand it receives and passes ascending bladder signals to higher brain centres and into the realm of conscious sensation. On the other hand it receives projections from many higher brain centres and also controls the primary input to the PMC; during bladder filling, therefore, such higher brain centres (particularly the prefrontal cortex[47]) can suppress the excitatory signal to the PMC and thus prevent voiding or incontinence; when voiding is consciously desired, they can allow the PMC to be excited.

Our understanding of the processing of bladder sensations in humans has been greatly advanced in recent years by the advent of functional brain imaging. Imaging studies have shown activation of the PAG during bladder filling[63,64] (FIG. 6); this is in keeping with its postulated role in receiving bladder afferents and relaying them (perhaps through the thalamus) to the insula, where normal visceral sensations, such as desire to void, are thought to be mapped[65]. Consistent with this postulate, the insula was active in most imaging studies of urine storage[66] and its activation apparently increased with bladder filling[67]. By contrast, bladder cooling did not significantly activate the PAG[68], suggesting that afferents related to noxious bladder stimulation might follow a different pathway to the thalamus and the cerebral cortex.

The PAG has multiple afferent and efferent connections, not only with the thalamus, the prefrontal cortex and the insula, but also with other higher brain centres. The influence of these centres — the anterior cingulate cortex particularly — probably determines how much attention

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one pays to signals coming from bladder afferents and how one reacts to them, whether by deciding to void or by recruiting mechanisms (for example, urethral sphincter contraction) that allow voiding to be postponed. The anterior cingulate cortex is an extensive region, and different parts were activated in different studies[66]. The dorsal part seems to be especially strongly activated by bladder distension in subjects with "poor bladder control" ([REF. 69]), suggesting a strong emotional reaction to a situation the subjects experienced as threatening. This pattern of abnormal activity might help to distinguish an abnormal sensation of urgency from a strong but normal desire to void.

Both clinical observations and observations from functional imaging strongly suggest that in humans the frontal lobes play an important part in determining the appropriateness of micturition. For example, the right inferior frontal gyrus, which is part of the prefrontal cortex, was active during storage in all the studies on which FIG. 6a is based[63,64]. The prefrontal cortex is thought to be the seat of planning complex cognitive behaviours and the expression of personality and appropriate social behaviour and has a role in attention and response-selection mechanisms[70]. It has strong and direct connections with the PAG[47], suggesting that it might be responsible for tonic suppression of voiding that is relaxed only when voiding is both desired and socially appropriate. In keeping with this postulate, in subjects who cannot sustain such suppression (that is, in subjects who have poor bladder control) the prefrontal cortex responds abnormally weakly to bladder filling[67]. The prefrontal cortex has multiple connections with the anterior cingulate gyrus[71] and both regions have direct or indirect connections with the PAG, the hypothalamus and other areas that are associated with autonomic control. The caudal hypothalamus has direct access to the PMC (FIG. 6b) and responded to changes in bladder volume or sensation in two imaging studies[69,72]. This might represent a further layer of control of the micturition reflex that permits voiding only if it is judged 'safe' to do so ([REF. 49]).

The existence of a pontine storage centre in humans (FIG. 5a) is not certain[54], but several imaging studies have shown activation near the expected location (that is, ventrolateral to the PMC) during storage or withholding of urine[66].

Bladder voiding

Animal studies have shown that reflex micturition is mediated by a spinobulbospinal pathway that passes through the PMC in the rostral brainstem[49,55,73] (FIG. 5b). Excitation of the PMC activates descending pathways that cause urethral relaxation and, some seconds later, activation of the sacral parasympathetic outflow. This results in contraction of the bladder and an increase in intravesical pressure and the flow of urine. Relaxation of the urethral smooth muscle is mediated by activation of the parasympathetic pathway to the urethra, which triggers the release of NO, and by the removal of adrenergic and somatic cholinergic excitatory inputs. Secondary reflexes elicited by the flow of urine through the urethra facilitate bladder emptying[1].

Single-unit recordings in cats and rats have revealed that several populations of PMC neurons exhibit firing that is correlated with reflex bladder activity[58,59,61,74–76]; these include neurons that are silent in the absence of bladder activity but fire prior to and during reflex bladder contractions (direct neurons); neurons that are active during the period between bladder contractions and are inhibited during contractions (inverse neurons); and neurons that fire transiently at the beginning and end of bladder contractions (on–off neurons). A large percentage of direct neurons project to the lumbosacral spinal cord, whereas only a small percentage of inverse neurons do. Thus, it has been speculated that inverse neurons function as local inhibitory neurons in the PMC. Both direct and inverse neurons exhibit excitatory synaptic responses to electrical stimulation of afferent axons in the pelvic nerve[58].

Functional imaging studies into the process of voiding in humans showed that the cortical and brainstem areas involved were comparable to those that are involved in cats: voiding was

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associated with activation in the prefrontal cortex, the insula, the hypothalamus, the PAG and in a region that is comparable to that of the PMC in cats[77,78]. In study participants who were unable to void, slightly different prefrontal activation was seen, together with a more ventral region of pontine activation that supported the existence of a pontine storage centre (see FIG. 5a). Another PET study confirmed the involvement of the insula, the PAG and the PMC in voiding[79]. These observations seem to be compatible with the concept outlined above — that voluntary voiding implies interruption of the tonic suppression (by the prefrontal cortex) of PAG input to the PMC.

Neurotransmitters

Various neurotransmitters have been implicated in the central control of the lower urinary tract. Putative excitatory transmitters include glutamic acid, tachykinins, pituitary-adenylate-cyclase-activating polypeptide, NO and ATP[61,80]. Glutamic acid, acting on NMDA (*N*-methyl-D-aspartate) and non-NMDA receptors, seems to be the essential transmitter in spinal and supraspinal reflex pathways that control the bladder and the external urethral sphincter[81–83]. Inhibitory amino acids (GABA (γ-aminobutyric acid) and glycine) and opioid peptides (enkephalins) exert a tonic inhibitory control in the PMC and regulate bladder capacity[1,62,84]. These substances also have inhibitory actions in the spinal cord. Some transmitters (dopamine, serotonin (5-hydroxytryptamine, 5-HT), noradrenaline, ACh and non-opioid peptides, including vasoactive intestinal polypeptide and corticotropin-releasing factor) have either inhibitory or excitatory effects, depending on the type of receptor that is activated, the receptors' location in the CNS and the species[83.84]. For example, dopamine elicits inhibitory effects on micturition through D_1-like receptors and facilitatory effects through D_2-like receptors. On the other hand, activation of 5-HT_{1A} receptors inhibits micturition in the cat but facilitates it in the rat[80].

Neuroplasticity and pathology

Developmental changes

The mechanisms that are involved in the storage and periodic elimination of urine undergo marked changes during prenatal and postnatal development[83,85]. In the fetus, before the nervous system has matured, urine is presumably eliminated from the bladder by non-neural mechanisms; however, at later stages of development voiding is regulated by primitive reflex pathways that are organized in the spinal cord. As the human CNS matures postnatally, reflex voiding is eventually brought under the modulating influence of higher brain centres (FIG. 7). In adults, injury or disease of the nervous system can lead to the re-emergence of primitive reflexes[86,87].

In many species (for example, rats and cats), voiding in neonates depends on an exteroceptive somato-bladder reflex mechanism that is triggered when the mother licks the genital or perineal region of the young animal. This reflex is organized in the sacral spinal cord and has an afferent limb in the pudendal nerve and an efferent limb in the pelvic nerve[85]. Similar reflexes have been identified in human infants. During the postnatal period this reflex becomes progressively weaker and is eventually replaced by an inhibitory perineal-to-bladder reflex and the adult form of reflex voiding[85], but spinal-cord injury in adult animals can cause the re-emergence of the excitatory somato-bladder reflex. The developmental and spinal-cord-injury-induced plasticity in sacral parasympathetic reflex pathways is due in part to alterations in glutamatergic excitatory transmission between interneurons and parasympathetic PGNs[42,58]. It has been proposed that these synaptic changes are due to competition between segmental and supraspinal inputs to the PGNs. Thus, synaptic remodelling in the sacral parasympathetic nucleus and in the brain is likely to be an important factor in the postnatal maturation of voiding reflexes.

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Suprapontine lesions

In humans, disruption of the suprapontine circuitry as a result of anterior cerebral lesions or the degeneration of dopaminergic neurons in Parkinson's disease removes tonic inhibitory control over the PMC, resulting in decreased bladder capacity and detrusor overactivity. Pharmacological studies in animals following decerebration or cerebral infarction have revealed that suprapontine lesions lead to upregulation of NMDA-glutamatergic and D2-dopaminergic excitatory mechanisms and downregulation of NMDA-glutamatergic and M_1-muscarinic inhibitory mechanisms in the brain[88,89]. Experimental cerebral infarction in rats also increases expression in the PMC of *Cox2* and the immediate early genes *c-fos* and *Zif268* ([REF. 89]), and these effects were blocked by an NMDA-glutamatergic antagonist. Injection of an RNA-synthesis inhibitor into the pons blocked the upregulation of *c-fos* and *Zif268* and suppressed the detrusor overactivity that was induced by cerebral infarction, suggesting that the effect of suprapontine lesions on bladder activity is mediated in part by changes in synaptic transmission in the PMC[89].

Spinal cord injury (SCI)

SCI rostral to the lumbosacral level eliminates voluntary and supraspinal control of voiding, leading initially to an areflexic bladder and complete urinary retention, followed by a slow development of automatic micturition and neurogenic detrusor overactivity (NDO) that is mediated by spinal reflex pathways[90]. However, voiding is commonly inefficient owing to simultaneous contractions of the bladder and the urethral sphincter (detrusor–sphincter dyssynergia) (FIG. 7c).

In cats with spinal lesions and disconnection of the sacral cord from brainstem centres, a segmental sacral spinal reflex emerges that drives reflex bladder contractions and is mediated by capsaicin-sensitive C-fibre afferents. This is the fundamental cause of reflex detrusor contractions in response to low-volume filling and of the underlying pathophysiology of NDO in experimental models[91] (FIG. 8). Sufficient clinical evidence exists to support the view that a comparable process occurs in humans following spinal-cord lesions, so there have been extensive efforts to therapeutically reduce the C-fibre afferent input. The emergence of C-fibre bladder reflexes seems to be mediated by several mechanisms, including changes in central synaptic connections and alterations in the properties of the peripheral afferent receptors that lead to sensitization of the ‘silent’ C-fibres and the unmasking of responses to mechanical stimuli[91,92].

In rats, bladder afferent neurons undergo both morphological[93] and physiological changes following SCI[94]; it has been speculated that this neuroplasticity is mediated by the actions of neurotrophic factors, such as nerve growth factor (NGF), that are released in the spinal cord or the urinary bladder[95–97]. Indeed, the production of neurotrophic factors increases in the bladder after SCI[95,96], and in rats chronic administration of NGF into the bladder induces bladder hyperactivity and increases the excitability of dissociated bladder afferent neurons. By contrast, intrathecal application of NGF antibodies suppressed neurogenic detrusor overactivity[96] and detrusor–sphincter dyssynergia[97] in SCI rats.

Animal and human studies also support a role for the suburothelial expression of TRPV1 ([REF. 98]), $P2X_3$ ([REF. 98]) and/or the sensory neuropeptides substance P (SP) and calcitonin-gene-related peptide (CGRP)[99] in the pathophysiology of human NDO, and patients with NDO have increased TRPV1- and $P2X_3$-immunoreactive suburothelial innervation compared with controls[100].

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Idiopathic detrusor overactivity (IDO)

Urgency incontinence with underlying IDO is a common condition, but its fundamental cause remains to be discovered. IDO probably has a number of pathogeneses depending on the patient's sex and age[101]. The hypothesis that IDO is myogenic was based on the finding that detrusor myocytes from people with IDO showed increased excitability and increased tendency for activity to spread between cells, resulting in coordinated myogenic contractions of the whole detrusor[102]. An alternative hypothesis proposed that the problem was neurogenic[103]. Subsequently a 'modular model' was suggested in which units of the bladder wall consisting of an area of smooth muscle supplied by either an intramural ganglia or possibly interstitial cells becomes hyperexcitable, so that physiological 'micromotions' become synchronous and cause involuntary detrusor contraction[104]. Most recently, Griffiths *et al.*[67] demonstrated, using functional MRI, that "poor bladder control" was associated with abnormally weak activation of the orbitofrontal cortex, suggesting a central cause. These hypotheses might not be mutually exclusive and the cause of IDO might vary according to the patient group and the type of IDO.

There is accumulating evidence that aberrant afferent activity plays an important part in IDO: compared with controls, women with IDO have an increased density of suburothelial nerve fibres that are immunoreactive for SP and CGRP[99], whereas men with detrusor overactivity that is associated with urethral obstruction have increased incidence of a positive ice-water test, which is thought to be related to activation of a C-fibre-afferent-evoked bladder reflex[105]. Moreover, intravesical administration of the TRPV1 agonist resiniferatoxin (RTX) delayed or suppressed involuntary detrusor contractions in patients with IDO[106], and biopsies from patients with IDO had increased expression of TRPV1 and $P2X_3$ that 'normalized' in response to botulinum A neurotoxin (BoNTX/A) treatment (see below)[100]. However, a recent study found that neurokinin-A-induced responses were impaired in detrusor muscle from patients with IDO but not from patients with neurogenic detrusor overactivity (NDO)[107]. It was concluded that IDO and NDO might have different pathophysiologies, although it remains unknown whether the findings reflect a consequence of other disorder-related factors or whether tachykinins (such as neurokinin A) are directly involved in the generation of some types of DO[108].

Cystitis and painful bladder conditions

Bladder pain and overactivity induced by cystitis have been attributed in part to changes in the electrical properties of capsaicin-sensitive C-fibre bladder afferent neurons. These neurons normally show phasic firing in response to prolonged depolarizing current pulses, whereas neurons isolated from rats with chronic chemically induced bladder inflammation exhibit tonic firing and a reduced threshold for the initiation of action potentials[109]. These changes have been linked to a reduction in a low-threshold A-type K^+ current (I_A) that controls neuronal excitability. Blockade of this K^+ current with 4-aminopyridine, heteropodatoxin or SP unmasks tonic firing in normal cells, whereas treatment with KW-7158, a drug that opens A-type K^+ channels, reverses this effect[110]. KW-7158 also reduces detrusor overactivity in rats with cystitis. NGF has been implicated in the mechanism of afferent sensitization because cystitis, like SCI, increases NGF expression in the bladder[111]. Chronic administration of NGF to the bladder or the spinal cord mimics the effect of chemically induced cystitis on I_A currents and firing in bladder afferent neurons[112].

Patch-clamp recordings in capsaicin-sensitive afferent neurons from cats with feline interstitial cystitis (FIC), a chronic naturally occurring painful bladder condition, revealed changes in I_A currents and firing that were similar to those described in rats with cystitis or rats that had been treated with NGF[113]. In addition, the currents that were induced by capsaicin were increased in amplitude and exhibited a slower desensitization[114]. The effects of capsaicin were normalized by treating the neurons with an inhibitor of protein kinase C that presumably leads

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to dephosphorylation of the capsaicin-sensitive channel TRPV1. These findings suggest that the bladder symptoms in cats with FIC are related in part to changes in K^+ and TRPV1 channels in sensory neurons.

Changes in the chemical communication between the urothelium and C-fibre afferent nerves might also be involved in afferent sensitization in cystitis. ATP excites sensory nerves by activating $P2X_{2/3}$ receptors, and bladder distension releases ATP from the urothelium (FIG. 2). In FIC cats[115] and patients[116] with interstitial cystitis, ATP release from urothelial cells is increased, raising the possibility that enhanced signalling between the urothelium and afferent nerves might trigger painful bladder sensations. Prostaglandins are also released from the urothelium and trigger hyperalgesia by acting through G-protein-coupled receptors and second-messenger pathways. This leads to changes in afferent excitability through phosphorylation of the $Na_v1.8$ Na^+ channel that generates tetrodotoxin-resistant Na^+ currents[117]. Down-regulation of $Na_v1.8$ expression in bladder afferent pathways reduced the bladder hyperactivity and immediate-early-gene expression in the spinal cord that was induced by chemical irritation of the bladder[118].

New therapies

Vanilloids

The rationale for using intravesical vanilloids to treat human detrusor overactivity was the demonstration in animal experiments that capsaicin-sensitive C-fibre afferents were functionally important in the pathogenesis of volume-determined reflex contractions[91,94,119]. The action of capsaicin and other vanilloids is mediated by TRPV1: activation of TRPV1results in membrane depolarization and massive release of sensory neuropeptides, which can lead to desensitization and cell death. Capsaicin initially excites C-fibres and then causes a period of prolonged desensitization[120]. The use of intravesical vanilloids in human NDO was therefore aimed at desensitizing bladder afferents[121]; prior instillation of a local anaesthetic reduced the capsaicin-induced irritation without blocking its effect[122]. A meta-analysis of the literature reported symptomatic and urodynamic improvement in 84% of NDO patients treated with intravesical capsaicin[123] (although it seems likely that there was ‘double counting’, and negative experiences had not been published). The authors subsequently showed that diluting capsaicin with glucidic acid improved tolerability of the treatment and that enduring symptomatic and urodynamic benefits were possible with this preparation[124].

RTX is a thousand times as neurotoxic as capsaicin but has equal pungency and can therefore produce the same effect at much greater dilutions. Uncontrolled studies showed that RTX was successful in treating NDO, but a large multi-centre placebo-controlled study using escalating doses failed to show clinical response in most of the treatment groups (although this was probably due to accidental inactivation of RTX during the administration of the solution). The effect of intravesical administration of vanilloids in patients with interstitial cystitis has also been disappointing. A multi-centre, randomized placebo-controlled trial using RTX showed no improvement over placebo in lower-urinary-tract functioning, pain levels and quality-of-life scores[125].

At the time of writing, despite the many positive reports of the clinical efficacy of these agents and the sound theoretical basis for their use, no licensed intravesical vanilloid therapy is currently available. However, it is thought that several pharmaceutical companies have development programmes in progress for agents that block the TRPV1 mechanism.

Botulinum toxin A

Injection of BoNT/A into the detrusor was introduced as a new treatment of intractable NDO on the theoretical basis that it would temporarily block the pre-synaptic release of ACh from

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the parasympathetic innervation and produce a paralysis of the detrusor smooth muscle[126]. Subsequent clinical results have exceeded all expectations, but the evidence so far suggests that it might have a more complex mechanism of action, through the inhibition of excitatory-neurotransmitter release from bladder afferents and urothelial cells[127] (FIG. 2).

In cultured rat DRG, BoNT/A induced a delayed, long-lasting inhibition of SP release and blocked neuronal glutamate release in an animal model of inflammatory pain[128], leading to a reduction in neurally mediated inflammation. In a rat model of spinal NDO, BoNT/A significantly reduced the abnormal distension-evoked urothelial release of ATP[129] and reduced the DO that was evoked by application of ATP or capsaicin in rat bladders *in vivo*[130].

Biopsies from a mixed population of NDO and IDO patients treated with intradetrusor BoNT/A showed no change in the overall suburothelial afferent-nerve density during the clinical response but a progressive decrease and, finally, normalization of $P2X_3$ and TRPV1 suburothelial nerve immunoreactivity, suggesting that BoNT/A affects the expression of sensory receptors in suburothelial nerve fibres[100]. $P2X_3$ immunoreactivity showed the fastest change, which correlated with improvements in patients' sensation of urgency.

By inhibiting urothelial ACh release, BoNT/A might block ACh's proposed excitatory effect on suburothelial afferent nerves, myofibroblasts or detrusor parasympathetic nerve endings during urine storage. Inhibition of the increased urothelial ATP release would reduce its proposed excitatory effect on suburothelial and urothelial $P2X_3$ receptors and P2Y receptors in the myofibroblast network. In addition, there might be an attenuation of central sensitization, leading to further peripheral desensitization through decreased central SP release.

As anticipated, BoNT/A's effect on efferent pathways is also significant. Both animal[131] and clinical studies show post-BoNT/A decreases in detrusor pressures during both filling and voiding, in conjunction with post-treatment increases in post-void residual urine volumes[126,132–134]. It seems likely that the exceptional efficacy of BoNT/A for the treatment of urgency incontinence is due to its combined effect on those intrinsic afferent and efferent systems that are pathologically up-regulated in detrusor overactivity.

Several studies have shown that the benefits of BoNT/A are maintained for 9–11 months on average[126,132] and that subsequent injections have comparable efficacy to the first, both in terms of the size of the effect and the duration of its action[134]. Furthermore, BoNT/A is as effective in patients with IDO[135–137] as it is in those with intractable NDO with spinal aetiology. Minimally invasive methods of delivering the injections in an outpatient setting[138] mean that this treatment will probably have far-reaching beneficial consequences for the treatment of incontinence.

Improved bladder emptying

Although therapies that improve bladder emptying in the context of prostatic hypertrophy are available, less attention has been given to the development of agents that are effective at treating the reduced urinary retention or incomplete emptying that are associated with neurological or functional disorders. This is because these conditions are not as prevalent as urinary incontinence, and because clean, intermittent self-catheterization already provides symptomatic relief; however, medication that could enhance efficient voiding would nevertheless be valuable.

Dense neuronal staining for NO synthase (NOS) has been identified in the urethral sphincters of animals and humans[139,140], and substantial animal experimental data show that NO is an important inhibitory neurotransmitter: its release results in sphincter relaxation during voiding. The hypothesis that augmentation of NO might be effective in reducing detrusor–sphincter

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dyssynergia following SCI[141] was tested using the NO donor isosorbide dinitrate. This produced a significant reduction in striated sphincter pressure at rest and during dyssynergic contraction, although there was no reduction in residual urine volume[142]. The use of a target-specific phosphodiesterase inhibitor might allow more subtle manipulation of the NO signalling cascade by reducing the breakdown of NO. However, sildenafil citrate, a selective phosphodiesterase type 5 (PDE-5) inhibitor, did not improve sphincter relaxation in women with a primary disorder of sphincter relaxation[143], possibly because the PDE-5 isoform that is targeted by this drug is not present in the female urethral sphincter.

Conclusion

During the past two decades, knowledge of the complex neural control of the apparently simple process of micturition has grown significantly. This has given us a better insight into the control of bladder storage and voiding in health and disease and a more complete understanding of the mode of action of existing therapies. The development of future treatments to reduce involuntary detrusor contraction and improve bladder emptying will doubtless be soundly based on this scientific understanding and be taken forward knowing that improvements in bladder control have a positive impact on patients' well-being.

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene

TRPV1 |

FURTHER INFORMATION

Derek Griffiths' homepage: http://ourworld.compuserve.com/homepages/nacs

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

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References

1. Morrison, J., et al. Incontinence. Abrams, P.; Cardozo, L.; Khoury, S.; Wein, A., editors. Health Publications Ltd; Jersey: 2005. p. 363-422.This book chapter provides a comprehensive review of the neural control of the lower urinary tract.
2. Fry, CH., et al. Incontinence. Abrams, P.; Cardozo, L.; Khoury, S.; Wein, A., editors. Health Publications Ltd; Jersey: 2005. p. 313-362.
3. de Groat, WC.; Booth, AM. Nervous Control of the Urogenital System (Autonomic Nervous System). Maggi, CA., editor. Vol. 3. Harwood Academic Publishers; London: 1993. p. 291-347.Ch. 9
4. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev 2004;84:935–986. [PubMed: 15269341]
5. Matsui M, et al. Mice lacking M2 and M3 muscarinic acetylcholine receptors are devoid of cholinergic smooth muscle contractions but still viable. J Neurosci 2002;22:10627–10632. [PubMed: 12486155]
6. Somogyi GT, Zernova GV, Yoshiyama M, Yamamoto T, de Groat WC. Frequency dependence of muscarinic facilitation of transmitter release in urinary bladder strips from neurally intact or chronic spinal cord transected rats. Br J Pharmacol 1998;125:241–246. [PubMed: 9786494]

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7. Burnstock, G. Purinergic and Pyrimidinergic Signalling II. Cardiovascular, Respiratory, Immune, Metabolic and Gastrointestinal Tract Function (Handbook of Experimental Pharmacology). Abbracchio, MP.; Williams, M., editors. Springer; Berlin: 2001. p. 423-515.
8. Janig W, Morrison JF. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res 1986;67:87–114. [PubMed: 3823484]
9. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. J Physiol 1990;425:545–562. [PubMed: 2213588]
10. Fall M, Lindström S, Mazieres L. A bladder-to-bladder cooling reflex in the cat. J Physiol 1990;427:281–300. [PubMed: 2213600]
11. Gosling JA, Dixon JS. Sensory nerves in the mammalian urinary tract. An evaluation using light and electron microscopy. J Anat 1974;117:133–144. [PubMed: 4844655]
12. Gabella G. The structural relations between nerve fibres and muscle cells in the urinary bladder of the rat. J Neurocytol 1995;24:159–171. [PubMed: 7798112]
13. Birder LA, et al. Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci USA 2001;98:13396–13401. [PubMed: 11606761]
14. Wiseman OJ, et al. The ultrastructure of bladder lamina propria nerves in healthy subjects and patients with detrusor hyperreflexia. J Urol 2002;168:2040–2045. [PubMed: 12394704]
15. Gabella G, Davis C. Distribution of afferent axons in the bladders of rats. J Neurocytol 1998;27:141–155. [PubMed: 10640174]
16. de Groat WC. The urothelium in overactive bladder: passive bystander or active participant? Urology 2004;64(Suppl. 1):7–11. [PubMed: 15621221]
17. Apodaca G. The uroepithelium: not just a passive barrier. Traffic 2004;5:117–128. [PubMed: 15086788] This is an excellent review of the properties of the urothelium.
18. Birder LA, et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nature Neurosci 2002;5:856–860. [PubMed: 12161756]
19. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder cells by hydrostatic pressure changes-a possible sensory mechanism? J Physiol 1997;505:503–511. [PubMed: 9423189] This was the first study to show the release of ATP from the urothelium.
20. Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A. Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology 2004;63(Suppl. 3A):17–23. [PubMed: 15013648]
21. de Groat WC. Integrative control of the lower urinary tract: preclinical perspective. Br J Pharmacol 2006;147(Suppl. 2):S25–S40. [PubMed: 16465182]
22. Hanna-Mitchell AT, et al. Non-neuronal acetylcholine and urinary bladder urothelium. Life Sci 2007;80:2298–2302. [PubMed: 17363007]
23. Beckel JM, Kanai A, Lee SJ, de Groat WC, Birder LA. Expression of functional nicotinic acetylcholine receptors in rat urinary bladder epithelial cells. Am J Physiol 2006;290:F103–F110.
24. Mansfield KJ, et al. Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: changes in ageing. Br J Pharmacol 2005;144:1089–1099. [PubMed: 15723094]
25. Tyagi S, et al. Qualitative and quantitative expression profile of muscarinic receptors in human urothelium and detrusor. J Urol 2006;176:1673–1678. [PubMed: 16952712]
26. Hawthorn MH, Chapple CR, Cock M, Chess-Williams R. Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility *in vitro*. Br J Pharmacol 2000;129:416–419. [PubMed: 10711338]
27. Braverman AS, Lebed B, Linder M, Ruggieri MR. M2 mediated contractions of human bladder from organ donors is associated with an increase in urothelial muscarinic receptors. Neurourol Urodyn 2007;26:63–70. [PubMed: 17123299]
28. Kanai A, et al. Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists. Am J Physiol 2007;292:1065–1072.
29. Andersson KE. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev 1993;45:253–308. [PubMed: 8248281]

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30. Rong W, Spyer KM, Burnstock G. Activation and senstitization of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. J Physiol 2002;541:591–600. [PubMed: 12042363]

31. Cockayne DA, et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in $P2X_3$-deficient mice. Nature 2000;407:1011–1015. [PubMed: 11069181] This paper provided an important demonstration of the functional importance of purinergic signalling in the bladder.

32. Sui GP, Rothery S, Dupont E, Fry CH, Severs NJ. Gap junctions and connexin expression in human suburothelial interstitial cells. BJU Int 2002;90:118–129. [PubMed: 12081783]

33. Wiseman OJ, Fowler CJ, Landon DN. The role of the human bladder lamina propria myofibroblast. BJU Int 2003;91:89–93. [PubMed: 12614258] In this paper, meticulous ultrastructural studies that identified myofibroblasts in the human bladder led to the hypothesis that these myofibroblasts form a structure that has the necessary characteristics to constitute the stretch receptor that signals bladder distension.

34. Wu C, Sui GP, Fry CH. Purinergic regulation of guinea pig suburothelial myofibroblasts. J Physiol 2004;559:231–243. [PubMed: 15235082]

35. Morgan CW, de Groat WC, Felkins LA, Zhang SJ. Intracellular injection of neurobiotin or horseradish peroxidase reveals separate types of preganglionic neurons in the sacral parasympathetic nucleus of the cat. J Comp Neurol 1993;331:161–182. [PubMed: 8509498]

36. Morgan CW, de Groat WC, Felkins LA, Zhang SJ. Axon collaterals indicate broad intraspinal role for sacral preganglionic neurons. Proc Natl Acad Sci USA 1991;88:6888–6892. [PubMed: 1713694]

37. Sasaki M. Morphological analysis of external urethral and external anal sphincter motoneurones of cat. J Comp Neurol 1994;349:269–287. [PubMed: 7860783]

38. Nadelhaft I, Vera PL, Card JP, Miselis RR. Central nervous system neurons labelled following the injection of pseudorabies virus into the rat urinary bladder. Neurosci Lett 1992;143:271–274. [PubMed: 1331903]

39. Vizzard MA, Erickson VL, Card JP, Roppolo JR, de Groat WC. Transneuronal labeling of neurons in the adult rat brainstem and spinal cord after injection of pseudorabies virus into the urethra. J Comp Neurol 1995;355:629–640. [PubMed: 7636036]

40. Birder LA, de Groat WC. Induction of *c-fos* gene expression of spinal neurons in the rat by nociceptive and non-nociceptive stimulation of the lower urinary tract. Am J Physiol 1993;265:R643–R648.

41. Birder LA, Roppolo JR, Erickson VL, de Groat WC. Increased *c-fos* expression in spinal lumbosacral projection neurons and preganglionic neurons after irritation of the lower urinary tract in the rat. Brain Res 1999;834:55–65. [PubMed: 10407093]

42. Araki I, de Groat WC. Synaptic modulation associated with developmental reorganization of visceral reflex pathways. J Neurosci 1997;17:8402–8407. [PubMed: 9334413]

43. Morgan C, Nadelhaft I, de Groat WC. The distribution of visceral primary afferents from the pelvic nerve to Lissauer's tract and the spinal gray matter and its relationship to the sacral parasympathetic nucleus. J Comp Neurol 1981;201:415–440. [PubMed: 7276258]

44. Steers WD, Ciambotti J, Etzel B, Erdman S, de Groat WC. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction. J Comp Neurol 1991;310:1–10. [PubMed: 1658087]

45. Thor KB, Morgan C, Nadelhaft I, Houston M, de Groat WC. Organization of afferent and efferent pathways in the pudendal nerve of the female cat. J Comp Neurol 1989;288:263–279. [PubMed: 2477417]

46. de Groat WC, et al. Neural control of the urethra. Scand J Urol Nephrol 2001;35(Suppl. 207):35–43.

47. Holstege G. Micturition and the soul. J Comp Neurol 2005;493:15–20. [PubMed: 16254993]

48. Sugaya K, Roppolo JR, Yoshimura N, Card JP, de Groat WC. The central neural pathways involved in micturition in the neonatal rat as revealed by the injection of pseudorabies virus into the urinary bladder. Neurosci Lett 1997;223:197–200. [PubMed: 9080466]

49. Blok B, Weer H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition centre or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. J Comp Neurol 1995;359:300–309. [PubMed: 7499530]

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50. Holstege G, Mouton LJ. Central nervous control of micturition. Int Rev Neurobiol 2003;56:123–145. [PubMed: 14696312]
51. Holstege G, Griffiths D, De Wall H, Dalm E. Anatomical and physiological observations on supraspinal control of bladder and urethral sphincter muscles in the cat. J Comp Neurol 1986;250:449–461. [PubMed: 3760249]
52. de Groat WC. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Paraplegia 1995;33:493–505. [PubMed: 8524601]
53. de Groat WC, Vizzard MA, Araki I, Roppolo JR. Spinal interneurons and preganglionic neurons in sacral autonomic reflex pathways. Prog Brain Res 1996;107:97–111. [PubMed: 8782515]
54. Griffths DJ. The pontine micturition centres. Scand J Urol Nephrol 2002;36(Suppl. 210):21–26.
55. de Groat WC, et al. Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine. J Auton Nerv Syst 1981;3:135–160. [PubMed: 6268684]
56. McMahon SB, Morrison JF. Spinal neurones with long projections activated from the abdominal viscera of the cat. J Physiol 1982;322:1–20. [PubMed: 7069608]
57. Ding YQ, et al. Direct projections from the lumbosacral spinal cord to Barrington's nucleus in the rat: a special reference to micturition reflex. J Comp Neurol 1997;389:149–160. [PubMed: 9390766]
58. de Groat WC, et al. Developmental and injury induced plasticity in the micturition reflex pathway. Behav Brain Res 1998;92:127–140. [PubMed: 9638955]
59. Sasaki M. Feed-forward and feedback regulation of bladder contractility by Barrington's nucleus in cats. J Physiol 2004;557:287–305. [PubMed: 15047771]
60. de Groat WC, Booth AM, Milne RJ, Roppolo JR. Parasympathetic preganglionic neurons in the sacral spinal cord. J Auton Nerv Syst 1982;5:23–43. [PubMed: 7056993]
61. Sugaya K, Nishijima S, Miyazato M, Ogawa Y. Central nervous control of micturition and urine storage. J Smooth Muscle Res 2005;41:117–132. [PubMed: 16006745]
62. Mallory BS, Roppolo JR, de Groat WC. Pharmacological modulation of the pontine micturition center. Brain Res 1991;546:310–320. [PubMed: 1676929]
63. Kavia R, DasGupta R, Fowler CJ. Functional imaging and central control of the bladder. J Comp Neurol 2005;493:27–32. [PubMed: 16255006] This is a comprehensive review of brain-imaging studies related to the CNS control of micturition.
64. DasGupta R, Kavia RB, Fowler CJ. Cerebral mechanisms and voiding function. BJU Int 2007;99:731–734. [PubMed: 17378838]
65. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nature Rev Neurosci 2002;3:655–666. [PubMed: 12154366]
66. Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn. Dec 18;2007 epub ahead of print.
67. Griffiths D, Derbyshire S, Stenger A, Resnick N. Brain control of normal and overactive bladder. J Urol 2005;174:1862–1867. [PubMed: 16217325]
68. Matsuura S, et al. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. J Urol 2002;168:2035–2039. [PubMed: 12394703]
69. Griffiths D, Tadic SD, Schaefer W, Resnick NM. Cerebral control of the bladder in normal and urge-incontinent women. Neuroimage 2007;37:1–7. [PubMed: 17574871]
70. Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. Nature 1991;349:61–64. [PubMed: 1985266]
71. Carmichael ST, Price JL. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 1995;363:615–641. [PubMed: 8847421]
72. Athwal BS, et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain 2001;124:369–377. [PubMed: 11157564]
73. Barrington FJ. The effects of lesions of the hind and midbrain on micturition in the cat. J Exper Physiol 1925;15:81–102.
74. Sugaya K, et al. Ascending and descending brainstem neuronal activity during cystometry in decerebrate cats. Neurourol Urodyn 2003;22:343–350. [PubMed: 12808711]
75. Tanaka Y, et al. Firing of micturition center neurons in the rat mesopontine tegmentum during urinary bladder contraction. Brain Res 2003;965:146–154. [PubMed: 12591131]

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76. Sasaki M. Properties of Barrington's neurones in cats: units that fire inversely with micturition contraction. Brain Res 2005;1033:41–50. [PubMed: 15680338]
77. Blok B, Willemsen T, Holstege G. A PET study of brain control of micturition in humans. Brain 1997;120:111–121. [PubMed: 9055802] This was the first brain-imaging study of micturition in humans.
78. Blok B, Sturms L, Holstege G. Brain activation during micturition in women. Brain 1998;121:2033–2042. [PubMed: 9827764]
79. Nour S, Svarer C, Kristensen JKI, Paulson OB, Law I. Cerebral activation during micturition in normal men. Brain 2000;123:781–789. [PubMed: 10734009]
80. de Groat WC, Yoshimura N. Pharmacology of the lower urinary tract. Ann Rev Pharmacol Toxicol 2001;41:691–721. [PubMed: 11264473] This is a comprehensive review of the pharmacology of the lower urinary tract.
81. Yoshiyama M, de Groat WC. Supraspinal and spinal α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and *N*-methyl-d-aspartate glutamatergic control of the micturition reflex in the urethane anesthetized rat. Neuroscience 2005;132:1017–1026. [PubMed: 15857706]
82. Chang HY, Cheng CL, Chen JJ, de Groat WC. Roles of glutamatergic and serotonergic mechanisms in reflex control of the external urethral sphincter in urethane-anesthetized rats. Am J Physiol 2006;291:R224–R234.
83. de Groat, WC.; Booth, AM.; Yoshimura, N. Nervous Control of the Urogenital System (Autonomic Nervous System). Maggi, CA., editor. Vol. 3. Harwood Academic Publishers; London: 1993. p. 227-289.Ch. 8
84. Andersson KE, Pehrson R. CNS involvement in overactive bladder: pathophysiology and opportunities for pharmacological intervention. Drugs 2003;63:2595–2611. [PubMed: 14636079]
85. de Groat WC. Plasticity of bladder reflex pathways during postnatal development. Physiol Behav 2002;77:689–692. [PubMed: 12527020]
86. Geirsson G, Fall M, Lindström S. The ice-water test-a simple and valuable supplement to routine cystometry. Br J Urol 1993;71:681–685. [PubMed: 8343894]
87. Jiang CH, Mazieres L, Lindstrom S. Cold- and menthol-sensitive C afferents of cat urinary bladder. J Physiol 2002;543:211–220. [PubMed: 12181293]
88. Yokoyama O, Yoshiyama M, Namiki M, de Groat WC. Changes in dopaminergic and glutamatergic excitatory mechanisms of micturition reflex after middle cerebral artery occlusion in conscious rats. Exp Neurol 2002;173:129–135. [PubMed: 11771945]
89. Yokoyama O, et al. RNA synthesis in pons necessary for maintenance of bladder overactivity after cerebral infarction in rat. J Urol 2003;169:1878–1884. [PubMed: 12686866]
90. de Groat WC, Yoshimura N. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Prog Brain Res 2005;152:59–84. [PubMed: 16198694]
91. de Groat WC, et al. Mechanisms underlying the recovery of urinary bladder function following spinal cord injury. J Auton Nerv Syst 1990;30(Suppl):S71–77. [PubMed: 2212495] This seminal work, which explained changes in bladder function following spinal cord injury, has been the basis for our current understanding of spinal neurogenic detrusor overactivity.
92. de Groat WC. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Paraplegia 1995;33:493–505. [PubMed: 8524601]
93. Kruse MN, Bray LA, de Groat WC. Influence of spinal cord injury on the morphology of bladder afferent and efferent neurons. J Auton Nerv Syst 1995;54:215–224. [PubMed: 7490423]
94. Yoshimura N, de Groat WC. Plasticity of Na^+ channels in afferent neurones innervating rat urinary bladder following spinal cord injury. J Physiol 1997;503:269–276. [PubMed: 9306271]
95. Vizzard MA. Neurochemical plasticity and the role of neurotrophic factors in bladder reflex pathways after spinal cord injury. Prog Brain Res 2006;152:97–116. [PubMed: 16198696] This is an excellent review of the contribution of neurotrophic factors to pathology-induced lower-urinary-tract dysfunction.
96. Seki S, et al. Immunoneutralization of nerve growth factor in the lumbosacral spinal cord reduces bladder hyperreflexia in spinal cord injured rats. J Urol 2002;168:2269–2274. [PubMed: 12394773]

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97. Seki S, et al. Suppression of detrusor-sphincter dyssynergia by immunoneutralization of nerve growth factor in lumbosacral spinal cord in spinal cord injured rats. J Urol 2004;171:478–482. [PubMed: 14665959]

98. Brady CM, et al. $P2X_3$-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. Eur Urol 2004;46:247–253. [PubMed: 15245821]

99. Smet P, Moore K, Jonavicius J. Distribution and colocalization of calcitonin gene-related peptide, tachykinins and vasoactive intestinal polypeptide in normal and idiopathic unstable human urinary bladder. Lab Invest 1997;77:37–49. [PubMed: 9251677]

100. Apostolidis A, et al. Decreased sensory receptors $P2X_3$ and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005;174:977–983. [PubMed: 16094018]

101. Milsom I, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760–766. [PubMed: 11412210]

102. Brading AF. A myogenic basis for the overactive bladder. Urology 1997;50(6A Suppl):57–67. [PubMed: 9426752]

103. de Groat W. A neurologic basis for the overactive bladder. Urology 1997;50(6A Suppl):36–52. [PubMed: 9426749]

104. Drake MJ, Mills IW, Gillespie JI. Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. Lancet 2001;358:401–403. [PubMed: 11502339]

105. Chai TC, Gray ML, Steers WD. The incidence of a positive ice water test in bladder outlet obstructed patients: evidence for bladder neural plasticity. J Urol 1998;160:34–38. [PubMed: 9628600]

106. Silva C, Ribeiro MJ, Cruz F. The effect of intravesical resiniferatoxin in patients with idiopathic detrusor instability suggests that involuntary detrusor contractions are triggered by C-fiber input. J Urol 2002;168:575–579. [PubMed: 12131313]

107. Sellers DJ, Chapple CR, Hay DPW, Chess-Williams R. Depressed contractile responses to neurokinin A in idiopathic but not neurogenic overactive human detrusor muscle. Eur Urol 2006;49:510–518. [PubMed: 16420969]

108. Andersson KE. Tachykinins: role in detrusor overactivity? Eur Urol 2006;49:423–425. [PubMed: 16426732]

109. Yoshimura N, de Groat WC. Increased excitability of afferent neurons innervating rat urinary bladder after chronic bladder inflammation. J Neurosci 1999;19:4644–4653. [PubMed: 10341262]

110. Sculptoreanu A, Yoshimura N, de Groat WC. KW-7158 enhances A-type K^+ currents in neurons of the dorsal root ganglion of the adult rat. J Pharmacol Exper Therap 2004;310:159–168. [PubMed: 15010502]

111. Vizzard MA. Changes in urinary bladder neurotrophic factor mRNA and NGF protein following urinary bladder dysfunction. Exper Neurol 2000;161:273–284. [PubMed: 10683293]

112. Yoshimura N, et al. Bladder overactivity and hyperexcitability of bladder afferent neurons after intrathecal delivery of nerve growth factor in rats. J Neurosci 2006;26:10847–10855. [PubMed: 17050722]

113. Sculptoreanu A, de Groat W, Buffington CAT, Birder LA. Protein kinase C contributes to abnormal capsaicin responses in DRG neurons from cats with feline interstitial cystitis. Neurosci Lett 2005;381:42–46. [PubMed: 15882787]

114. Sculptoreanu A, de Groat W, Buffington CAT, Birder LA. Abnormal excitability in capsaicin-responsive DRG neurons from cats with feline interstitial cystitis. Exper Neurol 2005;193:437–443. [PubMed: 15869946]

115. Birder LA, et al. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. Am J Physiol 2003;285:F423–F429.

116. Sun Y, Keay S, DeDeyne P, Chai TC. Augmented stretch activated adenosine triphosphate release from bladder uroepithelial cells in patients with interstitial cystitis. J Urol 2001;166:1951–1956. [PubMed: 11586266]

117. Lai J, Porreca F, Hunter JC, Gold MS. Voltage-gated sodium channels and hyperalgesia. Ann Rev Pharmacol Toxicol 2004;44:371–397. [PubMed: 14744251]

118. Yoshimura N, et al. The role of the tetrodotoxin-resistant sodium channel $Na_V1.8$ (PN3/SNS) in a rat model of visceral pain. J Neurosci 2001;21:8690–8696. [PubMed: 11606657]

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119. Cheng CL, Liu JC, Chang SY, Ma CP, de Groat WC. Effect of capsaicin on the micturition reflex in normal and chronic spinal cats. Am J Physiol 1999;277:R786–R794. [PubMed: 10484496]
120. Jancso N, Jancso-Gabor A, Szolcsanyi J. The role of sensory nerve endings in neurogenic inflammation induced in human skin and in the eye and paw of the rat. Br J Pharmacol Chemother 1968;33:32–41. [PubMed: 4298238]
121. Fowler CJ, Beck R, Gerrard S, Betts C. Intravesical capsaicin for treatment of detrusor hyperreflexia. J Neurol Neurosurg Psych 1994;57:169–173.This was the first clinical study to demonstrate the effectiveness of intravesical capsaicin administration in treating neurogenic detrusor overactivity.
122. Chandiramani VA, Petersen T, Duthie GS, Fowler CJ. Urodynamic changes during therapeutic intravesical instillations of capsaicin. Br J Urol 1996;77:792–797. [PubMed: 8705210]
123. de Seze M, et al. Intravesical instillation of capsaicin in urology: a review of the literature. Eur Urol 1999;36:267–277. [PubMed: 10473984]
124. de Seze M, et al. Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. J Urol 2004;171:251–255. [PubMed: 14665887]
125. Payne C, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double-blind, placebo, controlled trial. J Urol 2005;173:1590–1594. [PubMed: 15821499]
126. Schurch B, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000;164:692–697. [PubMed: 10953127] This was the first systematic report on the use of BoNT/A to treat NDO.
127. Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006;49:644–650. [PubMed: 16426734]
128. Cui M, Aoki KR. Botulinum toxin type A (BTX-A) reduces inflammatory pain in the rat formalin model. Cephalalgia 2000;20:414–420.
129. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int 2004;45:987–993. [PubMed: 15337297]
130. Atiemo H, et al. Effect of botulinum toxin on detrusor overactivity induced by intravesical adenosine triphosphate and capsaicin in a rat model. Urology 2005;65:622–626. [PubMed: 15780404]
131. Smith C, et al. Botulinum toxin A inhibits afferent nerve evoked bladder strip contractions. J Urol 2002;167:41.
132. Reitz A, et al. European experience of 200 cases treated with Botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004;45:510–515. [PubMed: 15041117]
133. Schurch B, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol 2005;174:196–200. [PubMed: 15947626]
134. Grosse J, Kramer G, Stohrer M. Success of repeat detrusor injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol 2005;47:653–659. [PubMed: 15826758]
135. Popat R, et al. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005;174:984–988. [PubMed: 16094019]
136. Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC. Botulinum A toxin injections into the detrusor: an effective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005;24:231–236. [PubMed: 15747344]
137. Schmid DM, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol 2006;176:177–185. [PubMed: 16753396]
138. Sahai A, Kalsi V, Khan MS, Fowler CJ. Techniques for the intradetrusor administration of botulinum toxin. BJU Int 2006;97:675–678. [PubMed: 16536751]

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139. Smet P, Jonavicius J, Marshall V, De Vente J. Distribution of nitric oxide synthase-immunoreactive nerves and identification of the cellular targets of nitric oxide in guinea-pig and human urinary bladder by cGMP immunohistochemistry. Neuroscience 1996;71:337–348. [PubMed: 9053789]

140. Ho KM, Borja MC, Persson K, Brading AF, Andersson KE. Expression of nitric oxide synthase immunoreactivity in the human female intramural striated urethral sphincter. J Urol 2003;169:2407–2411. [PubMed: 12771807]

141. Mamas MA, Reynard JM, Brading AF. Augmentation of nitric oxide to treat detrusor-external sphincter dyssynergia in spinal cord injury. Lancet 2001;357:1964–1967. [PubMed: 11425438]

142. Reitz A, Knapp PA, Muntener M, Schurch B. Oral nitric oxide donors: a new pharmacological approach to detrusor-sphincter dyssynergia in spinal cord injured patients? Eur Urol 2004;45:516–520. [PubMed: 15041118]

143. Datta SN, Kavia RB, Gonzales G, Fowler CJ. Results of double-blind placebo-controlled crossover study of sildenafil citrate (Viagra) in women suffering from obstructed voiding or retention associated with the primary disorder of sphincter relaxation (Fowler's Syndrome). Eur Urol 2007;51:489–497. [PubMed: 16884844]

144. de Groat, WC. Female Urology. 2nd. Raz, S., editor. Saunders; Philadelphia: 1996. p. 28-42.

145. Birder LA, de Groat WC. Mechanisms of disease: involvement of the urothelium in bladder dysfunction. Nature Clin Pract Urol 2007;4:46–54. [PubMed: 17211425]

Glossary

Pudendal nerve	A nerve that innervates the external genitalia and the urethral and anal sphincters
Detrusor muscle	The smooth muscle of the bladder
Onuf's nucleus	A nucleus in the sacral cord that contains the anterior horn cells that innervate the sphincters
Urothelium	The superficial layer of the bladder
Intravesical	Inside the bladder
Detrusor overactivity	In humans, involuntary detrusor contractions during bladder filling; in experimental animal, non-voiding detrusor contractions
Myofibroblast	A cell that has some characteristics of a fibroblast and some characteristics of a smooth-muscle cell also known as an interstitial cell.
Urethral reflexes	Involuntary autonomic and somatic neural mechanisms that control the urethral muscles
Urgency incontinence	Loss of urine that is immediately preceded by or accompanied by the sensation of urgency
Myogenic	Of muscle origin
Ice-water test	A test for bladder function in which ice water is instilled into the bladder to cause reflex detrusor contraction
4-aminopyridine	A molecule that is used to characterize subtypes of K^+ channel
Heteropodatoxin	A peptide that blocks voltage-gated K^+ channels

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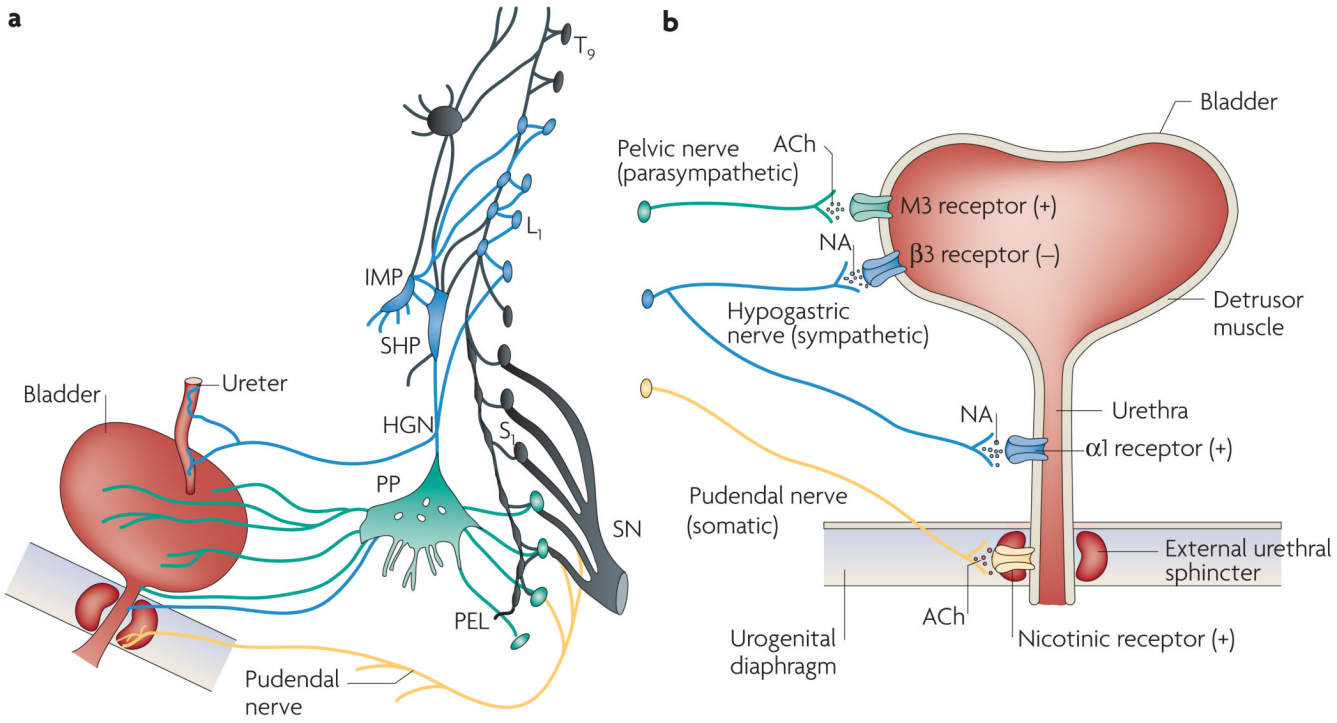

Figure 1. Efferent pathways of the lower urinary tract

a | Innervation of the female lower urinary tract. Sympathetic fibres (shown in blue) originate in the T11–L2 segments in the spinal cord and run through the inferior mesenteric ganglia (inferior mesenteric plexus, IMP) and the hypogastric nerve (HGN) or through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. Parasympathetic preganglionic fibres (shown in green) arise from the S2–S4 spinal segments and travel in sacral roots and pelvic nerves (PEL) to ganglia in the pelvic plexus (PP) and in the bladder wall. This is where the postganglionic nerves that supply parasympathetic innervation to the bladder arise. Somatic motor nerves (shown in yellow) that supply the striated muscles of the external urethral sphincter arise from S2–S4 motor neurons and pass through the pudendal nerves. **b** | Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M_3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release noradrenaline (NA), which activates β_3 adrenergic receptors to relax bladder smooth muscle and activates α_1 adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACh, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. Parasympathetic postganglionic nerves also release ATP, which excites bladder smooth muscle, and nitric oxide, which relaxes urethral smooth muscle (not shown). L_1, first lumbar root; S_1, first sacral root; SHP, superior hypogastric plexus; SN, sciatic nerve; T_9, ninth thoracic root. Part **a** modified, with permission, from [REF. 144] © (1996) W. B. Saunders Company.

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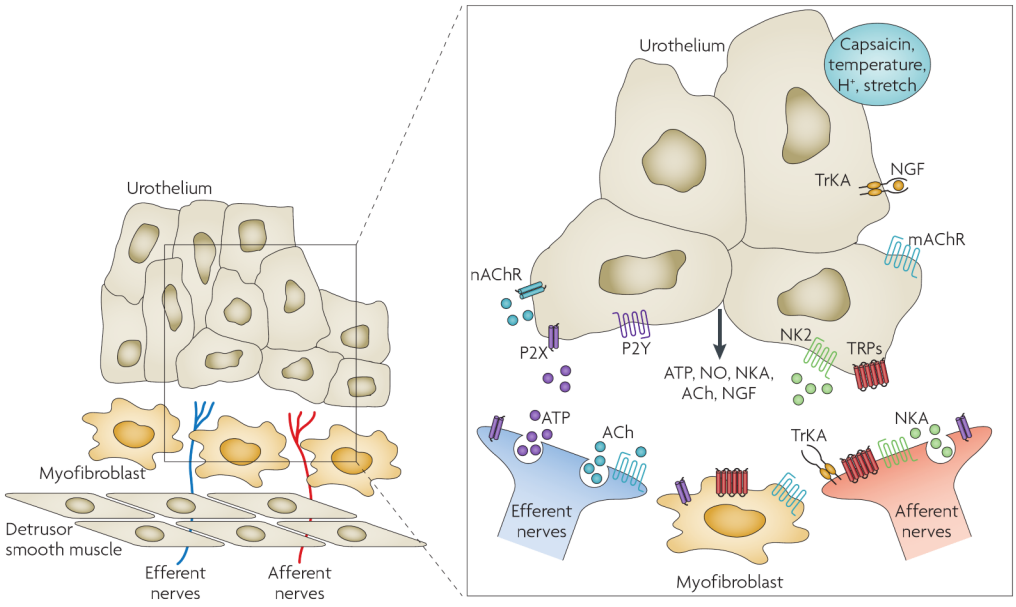

Figure 2. A model illustrating possible chemical interactions between urothelial cells, afferent nerves, efferent nerves and myofibroblasts in the urinary bladder

Urothelial cells, myofibroblasts and afferent nerves express common receptors, including purinergic receptors (P2X and P2Y) and transient-receptor-potential receptors (TRPs), such as the capsaicin receptor (TRPV1). Urothelial cells also express TRPV2, TRPV4 and TRMP8. Activation of receptors and ion channels in urothelial cells by bladder distension or chemical stimuli can release mediators, such as ATP, nitric oxide (NO), neurokinin A (NKA), acetylcholine (ACh) and nerve growth factor (NGF), that target adjacent nerves or myofibroblasts and might also act in an autocrine or paracrine manner on urothelial cells. Neuropeptides (including NKA) released from sensory nerves and the urothelium can act on the neurokinin 2 receptor (NK2) to sensitize the mechanoreceptive afferent nerve endings. NGF released from muscle or the urothelium can exert an acute and chronic influence on the excitability of sensory nerves through an action on tyrosine kinase A (TrkA) receptors. ATP released from efferent nerves or from the urothelium can regulate the excitability of adjacent nerves through purinergic P2X receptors. ACh released from efferent nerves or from the urothelium regulates the excitability of adjacent nerves through nicotinic or muscarinic ACh receptors (nAChR and mAChR). Figure modified, with permission, from [REF. 145] © (2007) Macmillan Publishers Ltd.

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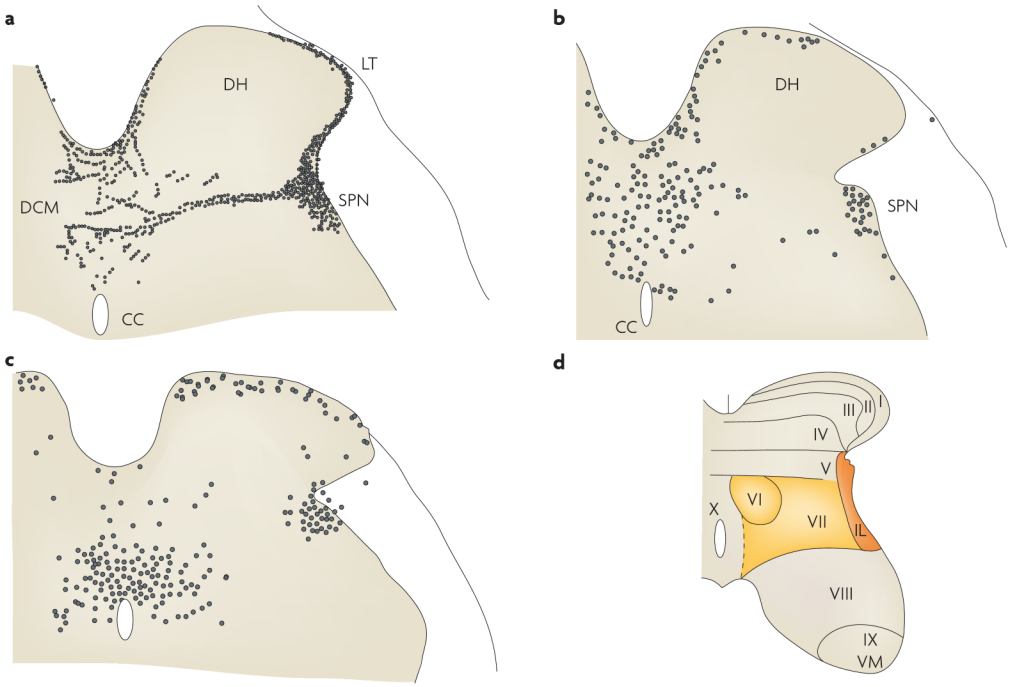

Figure 3. Primary afferent and spinal interneuronal pathways involved in micturition

a | Primary afferent pathways to the L6 spinal cord of the rat project to regions of the dorsal commissure (DCM), the superficial dorsal horn (DH) and the sacral parasympathetic nucleus (SPN) that contain parasympathetic preganglionic neurons. The afferent nerves consist of myelinated (Aδ) axons, which respond to bladder distension and contraction, and unmyelinated (C) axons, which respond to noxious stimuli. **b** | Spinal interneurons that express *c-fos* following the activation of bladder afferents by a noxious stimulus (acetic acid) to the bladder are located in similar regions of the L6 spinal segment. **c** | Spinal interneurons involved in bladder reflexes (labelled by transneuronal transport of pseudorabies virus injected into the urinary bladder) are localized to the regions of the spinal cord that contain primary afferents and *c-fos*. Some of these interneurons provide excitatory and inhibitory inputs to the parasympathetic preganglionic neurons located in the SPN. **d** | The laminar organization of the cat sacral spinal cord, showing the location of parasympathetic preganglionic neurons in the intermediolateral region of laminae V and VII (shaded area). CC, central canal; IL, intermediolateral nucleus; LT, Lissauer's tract; VM, ventromedial nucleus (Onuf's nucleus).

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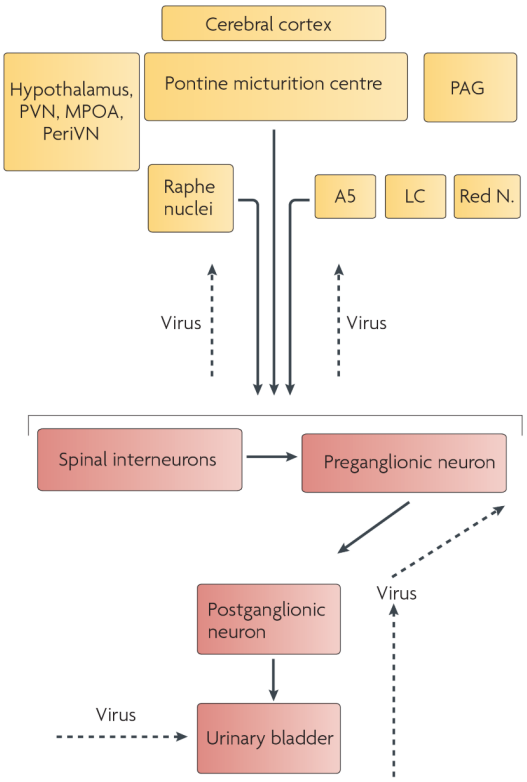

Figure 4. Connections between the lumbosacral spinal cord and brain areas involved in bladder control

The central pathways that are involved in controlling the urinary bladder can be visualized in rats using transneuronal virus tracing. Injection of pseudorabies virus into the wall of the urinary bladder leads to retrograde transport of the virus (indicated by the dashed arrows) and the sequential infection of postganglionic neurons, preganglionic neurons, spinal interneurons and then various supraspinal neural circuits that are synaptically linked to the spinal preganglionic neurons and interneurons. The supraspinal sites that are labelled by the virus transport include the pontine micturition centre (also known as Barrington's nucleus), the cerebral cortex, the paraventricular nucleus (PVN), the medial preoptic area (MPOA) and periventricular nucleus (PeriVN) of the hypothalamus, the periaqueductal grey (PAG), the locus coeruleus (LC) and subcoeruleus, the red nucleus (Red N.), the raphe nuclei and the A5 noradrenergic cell group. Synaptic connections are indicated by solid arrows. Synaptic inputs from supraspinal neurons can project to spinal preganglionic neurons or interneurons, as indicated by the bracket. Figure reproduced, with permission, from [REF. 21] © (2006) Macmillan Publishers Ltd.

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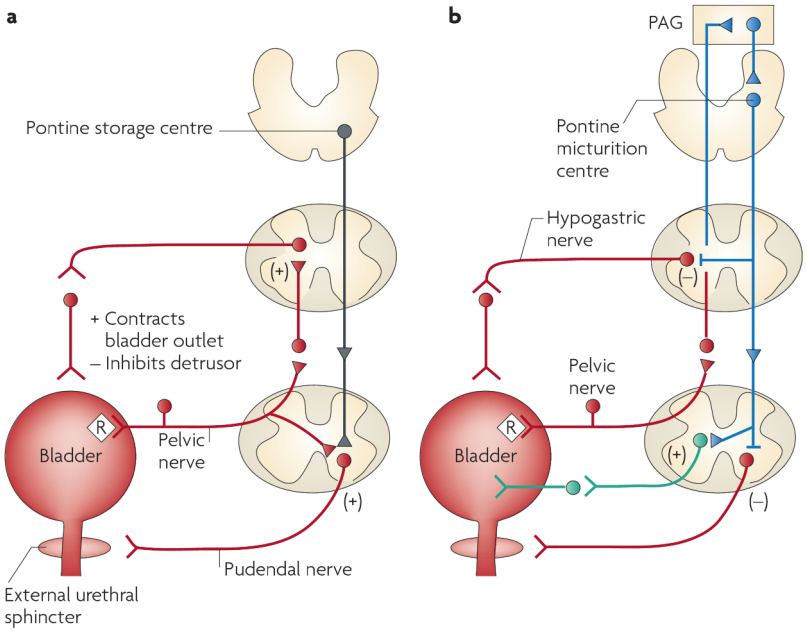

Figure 5. Neural circuits that control continence and micturition

a | Urine storage reflexes. During the storage of urine, distention of the bladder produces low-level vesical afferent firing. This in turn stimulates the sympathetic outflow in the hypogastric nerve to the bladder outlet (the bladder base and the urethra) and the pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle and modulates neurotransmission in bladder ganglia. A region in the rostral pons (the pontine storage centre) might increase striated urethral sphincter activity. **b** | Voiding reflexes. During the elimination of urine, intense bladder-afferent firing in the pelvic nerve activates spinobulbospinal reflex pathways (shown in blue) that pass through the pontine micturition centre. This stimulates the parasympathetic outflow to the bladder and to the urethral smooth muscle (shown in green) and inhibits the sympathetic and pudendal outflow to the urethral outlet (shown in red). Ascending afferent input from the spinal cord might pass through relay neurons in the periaqueductal grey (PAG) before reaching the pontine micturition centre. Note that these diagrams do not address the generation of conscious bladder sensations, nor the mechanisms that underlie the switch from storage to voiding, both of which presumably involve cerebral circuits above the PAG. R represents receptors on afferent nerve terminals.

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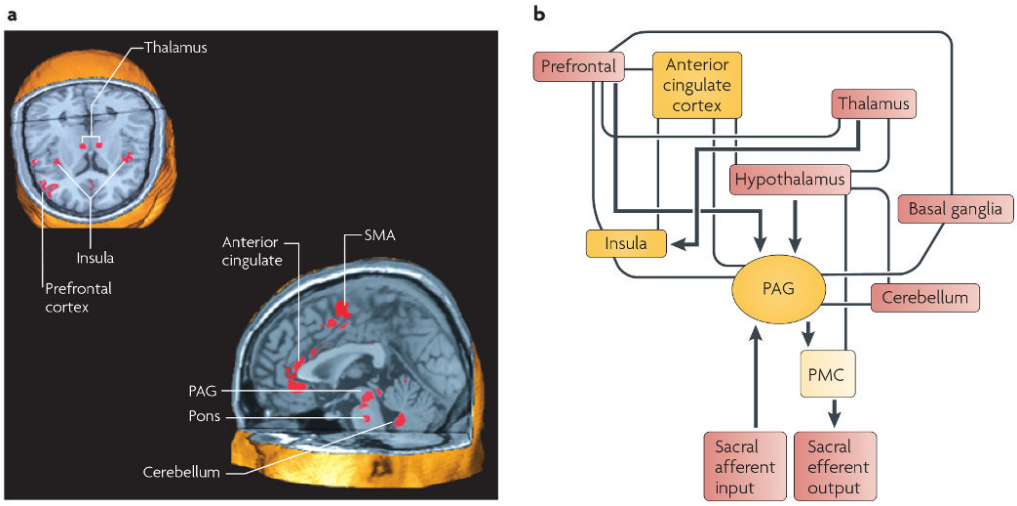

Figure 6. Brain areas involved in the regulation of urine storage

a | A meta-analysis of positron-emission tomography and functional MRI studies that investigated which brain areas are involved in the regulation of micturition reveals that the thalamus, the insula, the prefrontal cortex, the anterior cingulate, the periaqueductal grey (PAG), the pons, the medulla and the supplementary motor area (SMA) are activated during the urinary storage. **b** | A preliminary conceptual framework, based on functional brain-imaging studies, suggesting a scheme for the connections between various forebrain and brainstem structures that are involved in the control of the bladder and the sphincter in humans. Arrows show probable directions of connectivity but do not preclude connections in the opposite direction. Part **a** reproduced, with permission, from [REF. 64] © (2007) Backwell Science. Part **b** modified, with permission, from [REF. 63] © (2005) Wiley-Liss.

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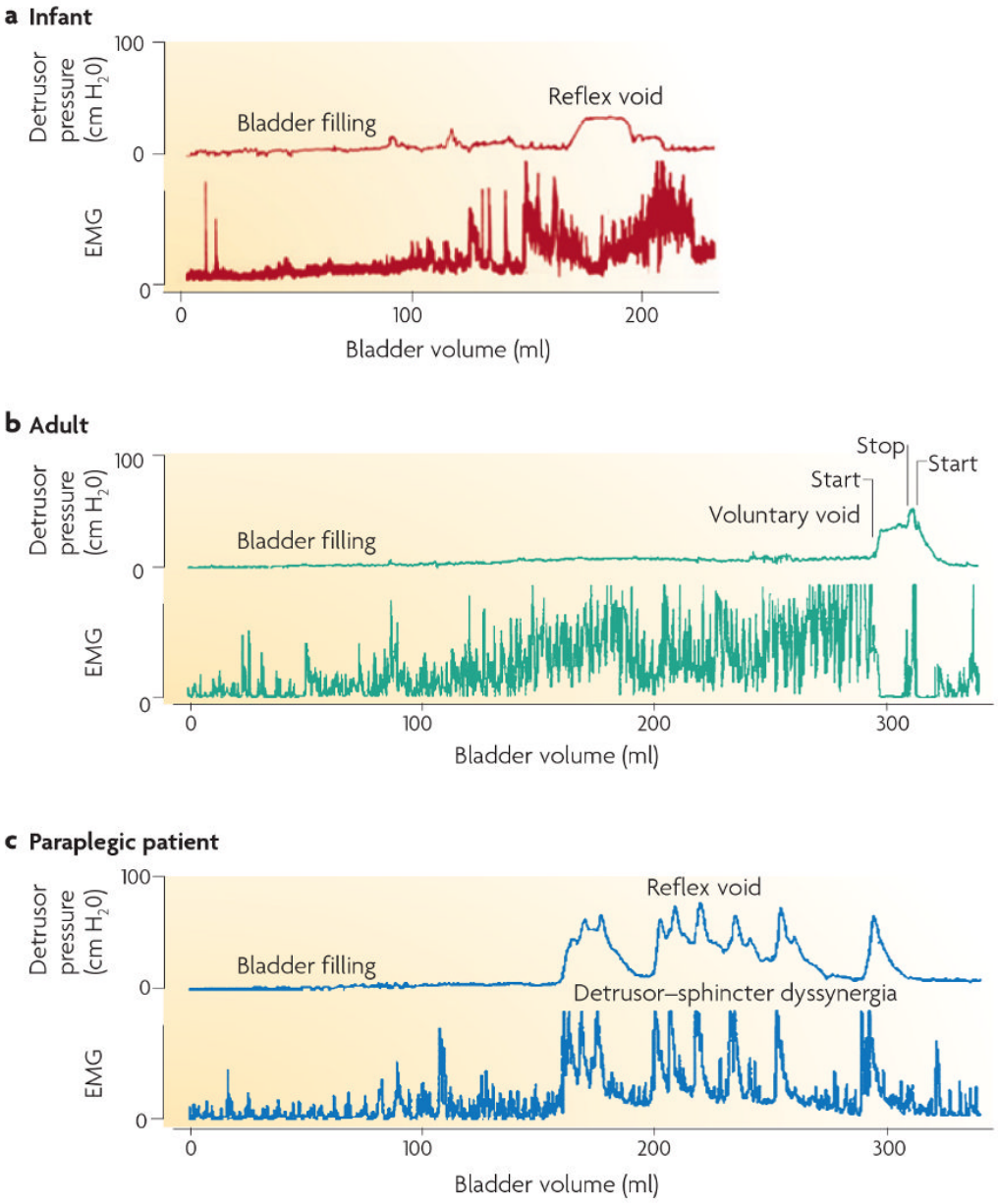

Figure 7. Reflex voiding responses in an infant, a healthy adult and a paraplegic patient

Combined cystometrograms and sphincter electromyograms (EMGs, recorded with surface electrodes), allowing a schematic comparison of reflex voiding responses in an infant (**a**) and in a paraplegic patient (**c**) with a voluntary voiding response in a healthy adult (**b**). The abscissa in all recordings represents bladder volume in millilitres; the ordinates represent electrical activity of the EMG recording and detrusor pressure (the component of bladder pressure that is generated by the bladder itself) in cm H_2O. On the left side of each trace (at 0 ml), a slow infusion of fluid into the bladder is started (bladder filling). In part **b** the start of sphincter relaxation, which precedes the bladder contraction by a few seconds, is indicated ('start'). Note that a voluntary cessation of voiding ('stop') is associated with an initial increase in sphincter EMG and detrusor pressure (a myogenic response). A resumption of voiding is associated with sphincter relaxation and a decrease in detrusor pressure that continues as the bladder empties and relaxes. In the infant (**a**) sphincter relaxation is present but less complete. On the other

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hand, in the paraplegic patient (**c**) the reciprocal relationship between bladder and sphincter is abolished. During bladder filling, involuntary bladder contractions (detrusor overactivity) occur in association with sphincter activity. Each wave of bladder contraction is accompanied by simultaneous contraction of the sphincter (detrusor–sphincter dyssynergia), hindering urine flow. Loss of the reciprocal relationship between the bladder and the sphincter in paraplegic patients thus interferes with bladder emptying.

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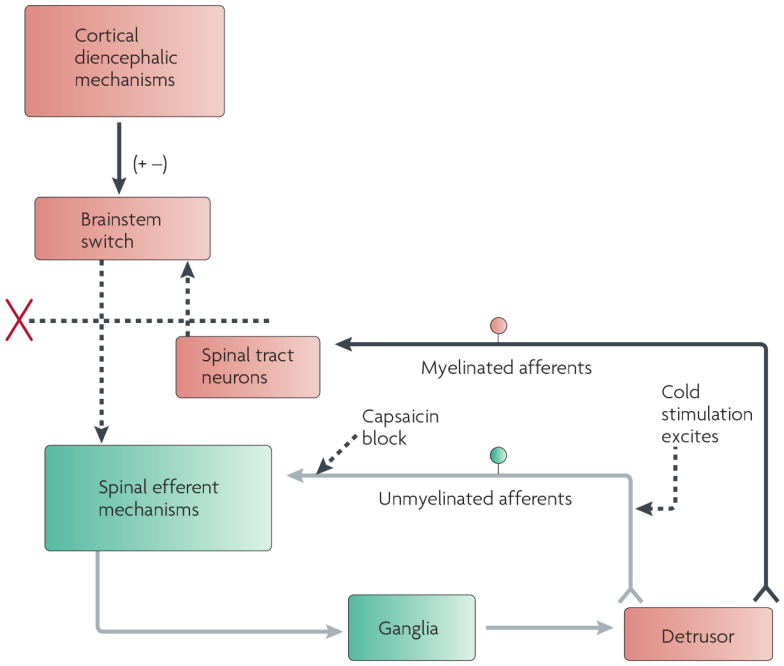

Figure 8. Organization of the parasympathetic excitatory reflex pathway to the detrusor muscle

This scheme is based on results from electrophysiological studies in cats. Micturition is initiated by a supraspinal reflex pathway that passes through a centre in the brainstem. The pathway is triggered by myelinated afferents (Aδ-fibres), which are connected to the tension receptors in the bladder wall. Injury to the spinal cord above the sacral segments interrupts the connections between the brain and spinal autonomic centres and initially blocks micturition. However, following cord injury a spinal reflex mechanism (shown in green) emerges that is triggered by unmyelinated vesical afferents (C-fibres); the A-fibre afferent inputs are ineffective. The C-fibre reflex pathway is usually weak or undetectable in animals with an intact nervous system. Stimulation of the C-fibre bladder afferents by installation of ice water into the bladder (cold stimulation) activates voiding responses in patients with spinal cord injury. Capsaicin (20–30 mg subcutaneously) blocks the C-fibre reflex in cats with spinal lesions but does not block micturition reflexes in intact cats. Intravesical capsaicin also suppresses detrusor hyperreflexia and cold-evoked reflexes in patients with neurogenic bladder dysfunction.