Received: 15 October 2023 | Accepted: 17 October 2023

DOI: 10.1002/nau.25316

INVITED REVIEW

Neurourology Urodynamics | SUFU | WILEY

How does the lower urinary tract contribute to bladder sensation? ICI-RS 2023

Luke Grundy[1] | **Jean J. Wyndaele**[2] | **Hikaru Hashitani**[3] | **Bahareh Vahabi**[4] | **Alan Wein**[5,6] | **Paul Abrams**[7] | **Basu Chakrabarty**[8] | **Christopher H. Fry**[8]

[1]Neurourology Research Group, Flinders Health and Medical Research Institute, Flinders University, South Australia, Australia

[2]Faculty GGW, University Antwerp, Antwerp, Belgium

[3]Department of Cell Physiology, Nagoya City University, Nagoya, Japan

[4]School of Applied Sciences, University of the West of England, Bristol, UK

[5]Perelman School of Medicine, Penn Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[6]Desai Sethi Institute of Urology, Miller School of Medicine, University of Miami, Miami, Florida, USA

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

[8]School of Physiology, Pharmacology & Neuroscience, University of Bristol, Bristol, UK

Correspondence
Luke Grundy, Flinders Centre for Innovation in Cancer (FCIC), Flinders University, Flinders Dr, Bedford Park SA5042, Australia.
Email: luke.grundy@flinders.edu.au

Funding information
Flinders Foundation

Abstract

Aim: Bladder sensation is critical for coordinating voluntary micturition to maintain healthy bladder function. Sensations are initiated by the activation of sensory afferents that innervate throughout the bladder wall. However, the physiological complexity that underlies the initiation of bladder sensory signaling in health and disease remains poorly understood. This review summarises the latest knowledge of the mechanisms underlying the generation of bladder sensation and identifies key areas for future research.

Methods: Experts in bladder sensory signaling reviewed the literature on how the lower urinary tract contributes to bladder sensation and identified key research areas for discussion at the 10th International Consultation on Incontinence—Research Society.

Results: The importance of bladder sensory signals in maintaining healthy bladder function is well established. However, better therapeutic management of bladder disorders with exaggerated bladder sensation, including overactive bladder syndrome (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS) is limited by a lack of knowledge in a number of key research areas including; the contribution of different nerves (pudendal, pelvic, hypogastric) to filling sensations in health and disease; the relative contribution of stretch sensitive (muscular) and stretch-insensitive (mucosal) afferents to bladder sensation in health and disease; the direct and indirect contributions of the muscularis mucosae to bladder contraction and sensation; and the impact of manipulating urothelial release factors on bladder sensation.

Conclusion: Disturbances in bladder sensory signaling can have severe consequences for bladder sensation and function including the development of OAB and IC/BPS. Advancing therapeutic treatments for OAB and IC/BPS requires a deeper understanding of the mechanisms underlying the generation of bladder sensation, and key areas for future research have been identified.

KEYWORDS
afferent, bladder, hypersensitivity, muscularis mucosae, nitric oxide, sensation, urothelium

1 | INTRODUCTION

Bladder sensation is critical for coordinating voluntary micturition to maintain healthy bladder function. Bladder sensations are initiated in the bladder wall, through the activation of sensory afferent nerves that innervate throughout the detrusor, lamina propria, and urothelium.[1,2] As the bladder fills with urine, and the bladder wall stretches to accommodate an increase in volume, afferent nerves are activated, and sensory signals are transduced into the central nervous system (CNS) to provide conscious awareness of bladder fulness.[1,3,4] As the volume of urine in the bladder continues to increase toward capacity there is a corresponding increase in the intensity of bladder sensation. Control of micturition is ultimately achieved via integration of bladder sensory signals with situational awareness and social cues to determine the appropriateness to urinate.[3] As such, exaggerated sensory signaling from the bladder can have severe consequences for bladder sensation and function, including the development of overactive bladder syndrome (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS).[5,6]

While our understanding of the importance of bladder sensory signals in maintaining healthy bladder function is well established, the physiological complexity that underlies the initiation of sensory signaling from the bladder in health and disease remains poorly understood. Developing a comprehensive understanding of bladder sensory signaling has the potential to dramatically improve the treatment of common urological disorders. As such, unraveling the intricate mechanisms and pathways responsible for bladder sensory signaling and bladder sensation is a crucial area for further research. A proposal at the 10th International Consultation on Incontinence–Research Society (ICI-RS-2023) meeting reviewed the literature, discussed new unpublished data, and proposed priority areas for future research that would lead to better therapeutic management of bladder disorders in which sensory abnormalities may be, at least in part, responsible. A comprehensive summary of the proposal and discussion is presented below.

2 | BLADDER SENSATION

Bladder sensations during health are generally restricted to relaying the intensity of bladder fullness. Bladder fullness increases in intensity as the bladder fills with urine from the first sensation of filling (FSF) to a first desire to void (FDV), and finally to a strong desire to void (SDV) (Table 1). These sensations have an obvious link to normal bladder function, such that conscious awareness of the degree of bladder fulness allows sentient animals, including humans, to effectively plan an appropriate moment to urinate. SDV may be considered as a protective sensation, and a crucial part of the bladder's physiological feedback mechanism to initiate urination, thereby avoiding bladder and upper tract damage, and thus maintain healthy bladder function over a lifetime. Technical evaluation of lower urinary tract (LUT) sensations in humans most commonly utilizes cystometric filling sensation assessment. Filling sensation during cystometry has been well studied, standardized, and found to be reliable and reproducible.[7] In humans, bladder filling elicits different types and grades of sensation which are integral to normal bladder function.[8] The clinical image of the evolving sensations during continued cystometry filling shows that a

TABLE 1 The description of the sensation, its location, the easiness to recognize, the ratio with SDV, and the evolution during different filling is given.

	Description of sensation	Location	Easiness to recognize as part of daily life	The ratio of SDV in neurologically normal	Evolution during further filling
FSF	Vague, waxing and waning	Lower pelvis	Not recognised	Appears at ±40% of SDV	It can be ignored for several minutes
FDV	Familiar: persuades a person to look for a place to void	Lower abdomen	Recognized	Appears at ±75% of SDV	Becomes gradually stronger and cannot be ignored
SDV	Constant, almost uncomfortable	Perineal/urethra	Recognized	=SDV	Uncomfortable, filling must be stopped

Note: The mean ratio of SDV should be interpreted with caution due to the extensive range.

Abbreviations: FDV, first desire to void; FSF, first sensation of filling; SDV, strong desire to void.

progressive increase in bladder volume translates into increased bladder sensation (Table 1). It Is hypothesized that differences in the location of the sensation, easiness to recognize, and the ratio of bladder fullness with SDV in healthy individuals may indicate the activation of distinct nerve populations and/or sensory afferent pathways to the spinal cord.

Bladder sensations that occur during various clinically distinct forms of cystitis, including bacterial, interstitial, or radio-, immuno-, and chemotherapy-induced cystitis are often described by patients in terms distinct from those experienced during healthy bladder function. Common patient-reported sensations include bladder pressure/pain, dysuria (pain/burning sensation when peeing), and urgency at lower bladder volumes compared to healthy subjects.[9,10] Intriguingly, these irritative symptoms are not clearly linked to exaggerated versions of bladder fullness but are entirely distinct sensations considered exclusive to bladder pathology. In the somatosensory system, irritative sensations present as pain and itch, and are crucial signifiers of tissue damage, infection, and inflammation that are necessary to evoke protective behavioral responses.[11] It could be hypothesized that the urgency, dysuria, and pain that are known to underlie the presence of infection and inflammation in the bladder have evolved to provide an awareness of bladder damage and initiate unique protective reflexes such as frequent urination.

It is currently unclear if different sensations, such as FSF, FDV, and SDV are carried by different nerves, for example, pelvic, hypogastric, and pudendal. Furthermore, it is not known if distinct pathways are responsible for relaying pathophysiological or irritative sensations, or if overlap exists between the generation of sensations at the upper extent of normal bladder function, such as SDV, and those of pathophysiology, for example, urgency as part of OAB. Furthermore, whether activation of sensory nerves within distinct anatomical locations within the bladder wall, such as the detrusor and/or the urothelium/lamina propria, are responsible for initiating distinct sensations has yet to be fully explored. These unknowns were discussed at length as part of a proposal at ICI-RS, with a focus on developing future research priorities to advance the field, discussed below.

3 | BLADDER AFFERENT INNERVATION

Bladder sensations are initiated via the activation of a complex network of sensory afferent nerves that innervate throughout the bladder wall. Bladder afferent nerves travel within the hypogastric, pelvic, and pudendal nerves that terminate within the thoracolumbar (TL) (T10-L1), lumbosacral (LS) (L6-S2), and sacral spinal cord (S2-S5), respectively[3] (Figure 1). Bladder afferents terminating within the dorsal horn of the spinal cord synapse with both reflex circuits that feed into efferent modulation of bladder wall contractility as well as second-order ascending projection neurons.[1,3] Ascending projection neurons from the spinal cord predominantly terminate within the periaqueductal gray (PAG) of the midbrain and thalamus from where signals are relayed to the somatosensory cortex and integrated with inputs from the limbic system to generate bladder sensations.[3,12]

Neuronal tracing studies in rodents have revealed most bladder afferents innervate the detrusor smooth muscle (~80%), and to a lesser extent the suburothelium and urothelium (~20%).[13,14] The urethra also displays a similar afferent fiber network, some of which are in direct contact with endocrine cells, paraneurones, that project into the urethral lumen.[15] These may constitute a mechanism to measure urine flow but will not be considered further here. Electrophysiological studies have classified bladder afferents by the location of their receptive fields and differential responses to mechanical stimuli (mucosal, muscular, muscular-mucosal)[16,17] (Figure 1). Detrusor (muscular) innervating afferents are well known to be crucial in translating confirmational changes in the bladder wall such as bladder distension and stretch into spinal cord activation and bladder sensation.[4] Nevertheless, the extent to which sensory perception is influenced by diverse afferent response attributes, encompassing mechanical activation thresholds (both low and high), conduction velocities (C fibers and Aδ fibers), adaptation rates (slow and fast adaptors), response variability (ranging from wide dynamic to saturated "nonencoding" afferents), response intensity (low and high responders), and neurochemical coding (peptidergic and nonpeptidergic), remains largely unresolved.[1,4,16,17] Furthermore, around 20% of afferents have been found innervating deeper into the bladder to terminate within the lamina propria and urothelium (termed mucosal afferents) and these afferents do not respond directly to bladder stretch.[16,17] As bladder distension is the primary stimulus for initiating bladder sensations, the relative importance of these mucosal afferents to bladder sensation in health and disease is currently unknown.

4 | ARE DIFFERENT NERVES RESPONSIBLE FOR GENERATING DIFFERENT FILLING SENSATIONS?

Based on observations made in patients where nerves had specifically been destroyed, a hypothesis was born suggesting that distinct major sensations related to

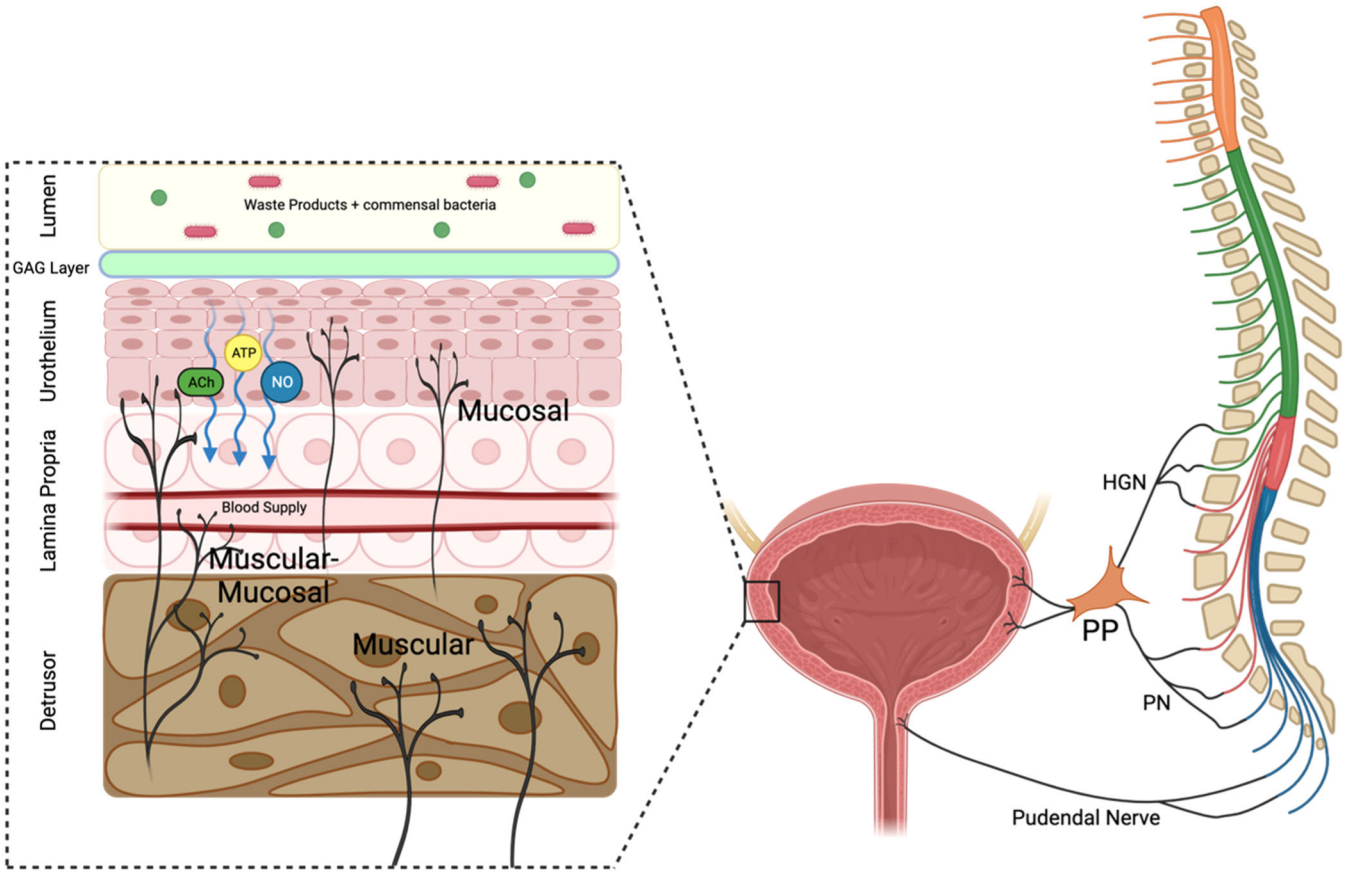

FIGURE 1 Sensory innervation of the bladder. Afferent nerves innervate throughout the bladder wall. Detrusor innervating afferents (muscular afferents) detect bladder stretch. Afferent nerves innervating the urothelium (mucosal afferents) do not respond to stretch, but may have a crucial role in detecting bladder inflammation, cell destruction, and neurotransmitters released from the urothelium. The urothelium releases an array of neurotransmitters during bladder stretch, including ATP, ACh, and NO, which can interact with bladder afferents, interstitial cells of the lamina propria, and urothelial cells. Muscular mucosal afferents respond to both bladder stretch and urothelial stroking. Sensory signals are relayed to the central nervous system via the hypogastric, pelvic, and pudendal nerves, which project to the dorsal horn of the thoracic, lumbar, and sacral spinal cord, respectively. Second-order neurons activated within the spinal cord synapse in the thalamus or the periaqueductal gray of the midbrain. Thalamic projections provide input into limbic and cortical structures to provide the emotional affective and conscious component of the voiding reflex pathway. Alterations in the intensity of sensory signals from the bladder can therefore have profound impacts on bladder sensation. ACh, acetylcholine; ATP, adenosine triphosphate; GAG, glycosaminoglycan; HGN, hypogastric nerve; NO, nitric oxide; PN, pelvic nerve; PP, pelvic plexus.

bladder filling—namely FSF, FDV, and SDV—may be associated with specific peripheral nerves. Notably, in cases of patients with nerve lesions resulting from unilateral or bilateral sacrum resection for tumor treatment, FSF was found to run through the hypogastric nerves.[18] Clinical studies also indicated that pelvic nerves might play a role in conveying the sensation of FDV,[19] while pudendal nerves relay SDV.[20] It is intriguing to note that even patients who have undergone surgery involving the spinal cord, bladder, or urethra, retain the ability to differentiate between the desire to void and the sensation that micturition is imminent.[21] Specifically, the sense of imminent micturition resides in the urethra, whereas the desire to void is associated with the stretching of the bladder wall (for detailed segmental distribution, refer to Table 2[22]). It is important to acknowledge, however, that the current body of evidence remains limited to small case series, and thus, definitive confirmation is lacking regarding whether distinct nerves are genuinely responsible for varying filling sensations in humans. Electrosensation evaluation by measuring the sensory threshold with electrical stimulation in the LUT is an excellent way to study the afferent innervation in specific peripheral nerves in humans. However, the nervous pathways are different from those of filling sensations, and electrosensation can thus not be used to evaluate sensations elicited by bladder filling.[23,24]

Preclinical studies in animals have provided some further insight into bladder sensory anatomy, however, while there is significant overlap in the anatomy of the

TABLE 2 The different sensations and the peripheral nerves they run (adapted in Wyndaele).

	Pelvic	Hypogastric	Pudendal
The sensation of filling	Yes	Probably	No
Desire to void	Yes	Probably	No
Strong desire to void	Possibly	Probably not	Yes
Pain bladder	Yes	Yes	No
Pain urethra	Probably	Probably not	Yes

LUT between animals and humans, the lack of sensory feedback limits extrapolation. The pelvic nerve is considered the major pathway for the transmission of sensory/afferent information from the bladder to the CNS in rodents. Comparing sensory nerve recordings from the pelvic and hypogastric nerves in rats reveals pelvic afferents exhibit significantly greater output in response to bladder filling than hypogastric nerves.[25] Furthermore, pelvic afferents on average have lower activation thresholds suggesting they may be more important in signalling early bladder sensations, while hypogastric afferents may be more relevant during greater levels of bladder distension.[25] Distinct differences in mechanical response characteristics have been identified between the hypogastric and pelvic nerves, including the proportions of peptidergic and nonpeptidergic neurons, and the proportion of neurons innervating the urothelium and muscle.[1,17,26] In-depth molecular characterization of bladder-innervating dorsal root ganglion (DRG) has reported molecular distinction between neuronal clusters originating from either thoracolumbar or lumbosacral DRG, with differential expression of key sensory ion channels and receptors.[27] Whether these clusters are correlated to distinct functional roles and/or anatomical distribution of afferents remains unknown but will be a crucial area for future research to identify specific therapeutic targets. Furthermore, whether the relative contribution of specific nerves to bladder sensation is altered in disease states is also unclear but will be crucial to the development of targeted therapeutics in the future.

5 | ARE MUCOSAL AND MUSCULAR NERVES RESPONSIBLE FOR GENERATING DISTINCT BLADDER SENSATIONS?

Bladder afferents innervating the detrusor smooth muscle (muscular afferents) respond directly to bladder stretch with an increase in afferent firing. Muscular afferent responses to stretch correlate well with the graded increase in sensation that are reported by humans during normal bladder filling.[4,8] As such, muscular afferents are likely to be the primary driver of bladder sensations that progress from fullness toward an SDV. Muscular afferents are sensitive not only to maintained changes of strain (stretch) of the bladder wall, but also have a dynamic response to transient spontaneous contractions.[28] Phasic spontaneous smooth muscle contractions trigger mechanosensitive afferent signals that have a much larger impact on afferent output than basal muscle tone rises, with activity that can often exceed the maximum afferent response that is generated during distension into supraphysiological ranges.[28,29] How afferent firing bursts during transient spontaneous contractions translate to sensation is unknown. However, there may be pathological consequences as the magnitude and frequency of spontaneous contractions can be particularly large in detrusor overactivity syndromes; for example, in neurogenic bladders associated with spinal cord injury. Thus, this constitutes a mechanism that could increase urgency sensations in overactive bladder conditions. Enhanced responses of stretch-sensitive afferents, either resulting from inflammation-induced sensitization or from alterations in the compliance of the bladder wall would also translate to exaggerated bladder sensation at lower bladder volumes.

In addition to stretch-sensitive afferents, we know that in rodents (mouse, rat, guinea pig) the bladder is also innervated by a variety of stretch-insensitive afferents, and their contribution to bladder sensation is currently unclear. Studying the anatomical location and functional properties of bladder afferents in humans represents a major technical and ethical challenge and has yet to be explored. However, in rodents, stretch-insensitive afferents have been broadly characterized based on their location innervating deeper into the bladder to terminate in the suburothelium and urothelium (mucosal afferents).[16,17] During normal bladder function, these afferents may play a key part in modulating bladder sensation by indirectly responding to bladder stretch through activation by mediators released from the urothelium[30] (discussed in further detail below) (Figure 1). These afferents may also play a crucial role in detecting cystitis, as we know that the inflammation associated with IC/BPS is primarily restricted to the mucosa and submucosa.[31] It is possible that mucosal afferents are uniquely tuned to detect urothelial damage and inflammation through the expression of distinct receptors and ion channels. This has yet to be fully investigated, but the lack of sensitivity to mechanical stretch confirms subtype specificity that has likely been driven by evolutionary pressure, such as the

rapid detection of infection. Limited evidence currently exists to support this novel hypothesis, but if true, the consequences for targeted treatment of bladder disorders with exaggerated sensation may be highly significant. A recent study showed that transient intravesical infusion of the potent TRPV1 agonist resiniferatoxin (RTX) into the bladder lumen silenced mucosal afferents and reversed cystitis-induced pain responses to bladder distension in vivo.[32] This concept was built on further at the ICI-RS meeting in 2023, where unpublished data was presented to show that mucosal, but not muscular afferents exhibit hypersensitivity in a mouse model of urinary tract infection.

If further studies confirm that mucosal afferents may have a major role in signaling during cystitis, this could have significant implications for future treatments of cystitis-related LUT symptoms. Being able to manipulate specific subpopulations of sensory nerves to relieve symptoms without impacting normal bladder function would represent a major step forward in the clinical management of bladder disorders including OAB and IC/BPS.

6 | HOW DOES THE UROTHELIUM/MUCOSA CONTRIBUTE TO BLADDER SENSATIONS?

6.1 | Direct interactions between confirmational changes in the mucosa and the activation of stretch sensitive afferents

While most mucosal afferents are stretch insensitive, a minority, known as muscular-mucosal afferents, exhibit responses to stretch and there is increasing interest in their role in regulating bladder afferent responses during distension.[16,17] While it is well known that the detrusor exhibits phasic contraction, a body of research now exists to show that the muscularis mucosae develops spontaneous contractions, and it is possible that the muscularis mucosae may contribute to mechanosensitive afferent signals directly via stretch evoked firing (only in human, pig, guinea-pig).[33] Intriguingly, isolated mucosa preparations, including muscularis mucosae, develop more than 10 times greater muscle force per cross-section area than detrusor smooth muscle, which may implicate the mucosa as a major source of sensory signaling.[34] It has been recently demonstrated that detrusor alone has very little intrinsic ability to generate spontaneous activity and an interaction between mucosa and detrusor is required for the generation of phasic contractions.[35] The nature of this mucosal–muscular interaction is currently unclear, however, recent unpublished data presented at ICI-RS showed physical attachment of the mucosa was necessary for the restoration of phasic contractions, and implied the presence of a diffusible factor released from the mucosa that induces detrusor spontaneous contractions.

The muscularis mucosae can also be more readily affected by urothelium- and blood-derived substances compared with detrusor because of its proximity to the urothelium and dense suburothelial capillary network. ATP, and other soluble mediators released from the urothelium may also interact with interstitial cells of the lamina propria to impact mucosal contractions and sensory output, although the interactive pathways remain to be elucidated. Differences in stretch- or chemosensitivity between muscularis mucosae and detrusor afferents could represent a therapeutic option. As removal of the mucosa impacts detrusor contractility, changes in mucosal contraction frequency and/or amplitude caused by urothelium- and blood-derived substances could directly impact detrusor contractility, and consequently impact sensory signaling initiated via muscular afferent endings.

6.2 | Indirect interactions between the urothelium, sensory nerves, and the bladder wall

There is accumulating evidence that urothelial chemical transduction mediates increases in bladder wall strain and raised afferent firing.[30,36] Various neurotransmitters, including adenosine triphosphate (ATP), acetylcholine (ACh), nitric oxide (NO•), and prostaglandins released from the urothelium have been proposed to activate and/or modulate the firing of bladder innervating sensory nerves or underlying bladder wall cells.[30] Receptors for these urothelial neurotransmitters are expressed on bladder-innervating sensory afferents, interstitial cells of the lamina propria, and the urothelium, providing the cellular architecture for autocrine or paracrine signaling of urothelial mediators to potentially influence bladder sensation and function.

ACh and ATP are released in response to mechanical stimuli, such as during bladder stretch, isolated mucosal preparation subjected to strain changes, or physiological shear forces applied to suspensions of isolated urothelium cells.[37,38] ACh release is more sensitive to applied mechanical forces than ATP and the two molecules show a facilitative autocrine/paracrine interaction as urothelial ATP release is attenuated by M2/M3 receptor antagonists and application of muscarinic agonists is sufficient to induce ATP release in the absence of strain changes.[39] It

is postulated that ATP is a final activator of afferent nerves as $P2X_3$ knock-out mice show a reduction in the firing rate to bladder filling, although there is a significant residual afferent response suggesting other signaling pathways, such as via detrusor afferent signaling, is still present.[40] NO• is also generated by the urothelium[41] and its release is associated with reduced afferent firing.[6] Exploitation of the NO• signaling pathway, via the activation of soluble guanylate cyclase (sGC) and cGMP generation, is considered below.

6.3 | Modulation of urothelial signal transduction during bladder pathologies and potential therapies

The association between urothelial/mucosal ATP release and afferent firing has stimulated research to characterize its release from pathological bladder tissues and investigate ways to reduce release. Increased ATP release from bladder wall tissue and isolated cell preparations has been measured in several LUT disorders (summarised in Winder et al.[30]), although the cellular routes are unclear. In addition, a greater ATP release is associated with increased fibrosis and loss of bladder wall compliance. This prompted the hypothesis that stretch-induced ATP release is not a function of the extent of bladder length (strain) per se, but of the raised internal tension (stress) upon stretch.[39] Indeed, this is similarly observed in ex-vivo afferent recordings, whereby reduced bladder compliance is associated with increased afferent output. Thus, antifibrotic therapies offer one route to reduce ATP release and hence urgency symptoms that are associated with bladder filling.

Manipulation of the NO• signaling pathway, in particular, raising cellular cGMP levels, offers a treatment paradigm to manipulate stress-induced ATP release. One intervention is to reduce breakdown of cGMP by selective inhibition of the phosphodiesterase type-5 (PDE5) enzyme with agents such as sildenafil or tadalafil. Another is to activate sGC enzymic activity to generate more cGMP, especially useful when activity has been reduced by oxidative stress—an example is the sGC activator, cinaciguat. Several lines of evidence suggest this is a useful approach. First, sildenafil and cinaciguat have antifibrotic actions on the bladder wall associated with outflow tract obstruction or aging[42,43] and so would reduce distension-induced ATP-release after normalization of bladder wall compliance. Second, sildenafil or cinaciguat also reduce ATP release from isolated urothelial cells (unpublished data), or from stretch-activated mucosa preparations.[44] Furthermore, sildenafil reduces ATP release from the mucosal surface of bladder wall preparations subjected to changes of transmural pressure under normal conditions or treated with lipopolysaccharide to enhance ATP release.[45] Third, tadalafil, or a NO• precursor, L-arginine, reduced A-delta and C-fibre nerve activity induced by bladder wall distension as well as hyperactivity generated by inflammatory agents, such as acrolein or cyclophosphamide.[46]

Overall, there is compelling evidence to suggest a link between the release of chemical mediators from urothelial cells and increased afferent firing, including ATP. Enhancement of release may be the basis of increased bladder wall sensations for LUT pathologies. Manipulation of intracellular cGMP levels, to downregulate ATP release offers one potential therapeutic route to alleviate urgency symptoms.

7 | RESEARCH QUESTIONS AND CONCLUSIONS

Healthy bladder function is crucial for quality of life, yet a significant proportion of the population have chronic functional urological disorders characterized by exaggerated bladder sensation that are not adequately managed by currently available therapeutics. Unraveling the physiological complexity that underlies the initiation of sensory signaling and the subsequent generation of debilitating symptoms during bladder disorders will be a crucial step toward appropriate therapeutic management. However, while the ICI-RS-2023 delegation highlighted important progress in the field, significant knowledge gaps remain, and key research questions remain to be answered (Table 3).

For some research questions, the methodology is clear, and it is only a matter of time before further knowledge is elucidated on the autocrine and paracrine signaling that occurs within the bladder wall to regulate interactions between the cells of the urothelium, mucosa, and detrusor. A greater challenge will be understanding how alterations in the sensory neurobiology of the bladder translates to altered sensation. Assessing sensation requires whole intact systems, and thus live subjects, which for obvious ethical reasons cannot be easily performed in humans without significant technological breakthroughs. Furthermore, interpreting the results of preclinical animal studies is fundamentally limited by the ability of animals, most commonly rodents, to report sensations and the added assumption that animals cannot contextualize sensation in the same way as humans. The most common way to assess changes in sensation or sensory signaling is electrophysiologically via the visceromotor response to bladder distension in vivo, assessing spinal cord activation following in vivo

TABLE 3 Key research questions resulting from discussions during ICI-RS 2023.

Research questions
Are different nerves responsible for different filling sensations in humans?
Are different nerves responsible for relaying pathophysiological sensations?
Is the relative contribution of specific nerves to bladder sensation altered in disease states?
How do afferent response characteristics contribute to different bladder sensations?
What is the role of stretch insensitive afferents to bladder sensation in health and disease?
How could mucosal contractility (not mucosa-derived substances) alter detrusor contractility?
Which mucosal-derived substances are responsible for regulating spontaneous detrusor contractility?
How do afferent firing bursts during transient spontaneous contractions translate to sensation?

Abbreviation: ICI-RS, International Consultation on Incontinence–Research Society.

bladder distension, or by recording the sensory output directly from the bladder-innervating afferent nerves ex vivo or in vivo. As highlighted at ICI-RS 2023, however, it remains unclear which sensory nerves (hypogastric, pelvic, pudendal) and regions of the spinal cord (thoracolumbar, lumbosacral, sacral) are most important to bladder sensation in health and disease. As such, the translation of preclinical findings to humans remains a major challenge to clinical progress.

Understanding the specific nerve populations and/or pathways responsible for sensation in health and pathophysiology could have profound implications for future therapeutic interventions for bladder disorders and should be a key priority for future urology research. Being able to target specific nerves directly or indirectly via anatomical location, receptor expression, or neurochemistry could translate to more effective neuromodulation and pharmacological targeting, leading to increased therapeutic efficacy in the absence of side effects.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and writing of this review. All authors contributed to discussions at or after the ICI-RS 2023. Luke Grundy, Jean J. Wyndaele, Hikaru Hashitani, Bahareh Vahabi, Basu Chakrabarty, and Christopher H. Fry performed initial literature searches, wrote, and drafted the initial manuscript, tables, and figures. All authors edited the final manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

Funding for this study was provided by a Flinders Foundation Fellowship awarded to L. G. Travel support to attend ICI-RS 2023 was provided by Flinders Health and Medical Research Institute. Open access publishing facilitated by Flinders University, as part of the Wiley - Flinders University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

P. A.: Consultant to: Astellas, Teva, Sandoz, Coloplast; Lecturer for: Astellas, Cipla, Sun Pharma, Ferring. The remaining author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

No new data has been generated for this manuscript.

ORCID

Jean J. Wyndaele http://orcid.org/0000-0002-0879-6854
Hikaru Hashitani http://orcid.org/0000-0002-3877-4349
Bahareh Vahabi http://orcid.org/0000-0002-7186-0943
Paul Abrams http://orcid.org/0000-0003-2776-2200
Basu Chakrabarty http://orcid.org/0000-0002-7320-4931
Christopher H. Fry http://orcid.org/0000-0003-3647-5983

REFERENCES

1. de Groat WC, Yoshimura N. Afferent nerve regulation of bladder function in health and disease. *Handb Exp Pharmacol*. 2009;194:91-138.
2. de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. *Compr Physiol. A*. 2015;5(1):327-396.
3. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. *Nat Rev Neurosci*. 2008;9(6):453-466.
4. Grundy L, Harrington AM, Caldwell A, et al. Translating peripheral bladder afferent mechanosensitivity to neuronal activation within the lumbosacral spinal cord of mice. *Pain*. 2019;160(4):793-804.
5. Grundy L, Caldwell A, Brierley SM. Mechanisms underlying overactive bladder and interstitial cystitis/painful bladder syndrome. *Front Neurosci*. 2018;12:931.
6. Daly DM, Collins VM, Chapple CR, Grundy D. The afferent system and its role in lower urinary tract dysfunction. *Curr Opin Urol*. 2011;21(4):268-274.
7. Drake MJ, Doumouchtsis SK, Hashim H, Gammie A. Fundamentals of urodynamic practice, based on International Continence Society good urodynamic practices recommendations. *Neurourol Urodyn*. 2018;37(S6):S50-S60.
8. Wyndaele JJ. A clinical study on subjective sensations during bladder filling. *Int Urogynecol J*. 1991;2(4):215-218.
9. Berry SH, Elliott MN, Suttorp M, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol*. 2011;186(2):540-544.

10. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. *J Urol*. 2013;189(1):141-145.
11. Garland EL. Pain processing in the human nervous system. *Prim Care*. 2012;39(3):561-571.
12. Athwal BS, Berkley KJ, Hussain I, et al. Brain responses to changes in bladder volume and urge to void in healthy men. *Brain*. 2001;124(2):369-377.
13. Spencer NJ, Greenheigh S, Kyloh M, et al. Identifying unique subtypes of spinal afferent nerve endings within the urinary bladder of mice. *J Comp Neurol*. 2018;526(4):707-720.
14. Smith-Anttila CJA, Morrison V, Keast JR. Spatiotemporal mapping of sensory and motor innervation of the embryonic and postnatal mouse urinary bladder. *Dev Biol*. 2021;476:18-32.
15. Iwanaga T, Takahashi-Iwanaga H. Anatomical background of the sensory function in the urethra: involvement of endocrine paraneurons and afferent nerves in divergent urogenital functions. A review. *Biomed Res*. 2022;43(6):187-199.
16. Zagorodnyuk VP, Gibbins IL, Costa M, Brookes SJH, Gregory SJ. Properties of the major classes of mechanoreceptors in the guinea pig bladder. *J Physiol*. 2007;585(1):147-163.
17. Xu L, Gebhart GF. Characterization of mouse lumbar splanchnic and pelvic nerve urinary bladder mechanosensory afferents. *J Neurophysiol*. 2008;99(1):244-253.
18. Gunterberg B, Norlén L, Stener B, Sundin T. Neurourologic evaluation after resection of the sacrum. *Invest Urol*. 1975;13(3):183-188.
19. Learmonth JR. A contribution to the neurophysiology of the urinary bladder in man. *Brain*. 1931;54(2):147-176.
20. Mundy AR. Clinical physiology of the bladder, urethra and pelvic floor. In: Mundy AR, Stephenson AJ, Wein AJ, eds. *Urodynamics, principles, practice and application*. Churchill Livingstone; 1984:14-25.
21. Nathan PW. Sensations associated with micturition. *Br J Urol*. 1956;28(2):126-131.
22. Wyndaele JJ, ed. Neurophysiology of pelvic sensation. *Sensation in the pelvic region*. Springer International Publishing; 2022:3-12.
23. De Wachter S, Wyndaele JJ. Can the sensory threshold toward electrical stimulation be used to quantify the subjective perception of bladder filling? A study in young healthy volunteers. *Urology*. 2001;57(4):655-658; discussion 658-659.
24. Wyndaele JJ, Wyndaele M. Combining different evaluations of sensation to assess the afferent innervation of the lower urinary tract after SCI. *Spinal Cord*. 2021;59(2):201-206.
25. Moss NG, Harrington WW, Tucker MS. Pressure, volume, and chemosensitivity in afferent innervation of urinary bladder in rats. *Am J Physiol*. 1997;272(2):R695-R703.
26. Clodfelder-Miller B, DeBerry JJ, Ness TJ. Urothelial bladder afferents selectively project to L6/S1 levels and are more peptidergic than those projecting to the T13/L1 levels in female rats. *Heliyon*. 2023;9(8):e18495.
27. Meerschaert KA, Adelman PC, Friedman RL, Albers KM, Koerber HR, Davis BM. Unique molecular characteristics of visceral afferents arising from different levels of the neuraxis: location of afferent somata predicts function and stimulus detection modalities. *J Neurosci*. 2020;40(38):7216-7228.
28. McCarthy CJ, Zabbarova IV, Brumovsky PR, Roppolo JR, Gebhart GF, Kanai AJ. Spontaneous contractions evoke afferent nerve firing in mouse bladders with detrusor overactivity. *J Urol*. 2009;181(3):1459-1466.
29. Grundy L, Chess-Williams R, Brierley SM, et al. NKA enhances bladder-afferent mechanosensitivity via urothelial and detrusor activation. *Am J Physiol Renal Physiol*. 2018;315(4):F1174-F1185.
30. Winder M, Tobin G, Zupančič D, Romih R. Signalling molecules in the urothelium. *BioMed Res Int*. 2014;2014:1-14.
31. Grover S, Srivastava A, Lee R, Tewari AK, Te AE. Role of inflammation in bladder function and interstitial cystitis. *Ther Adv Urol*. 2011;3(1):19-33.
32. Ramsay S, Keightley L, Brookes S, Zagorodnyuk V. TRPV1 and TRPM8 antagonists reduce cystitis-induced bladder hypersensitivity via inhibition of different sensitised classes of bladder afferents in guinea pigs. *Br J Pharmacol*. 2023;180(11):1482-1499.
33. Mitsui R, Lee K, Uchiyama A, et al. Contractile elements and their sympathetic regulations in the pig urinary bladder: a species and regional comparative study. *Cell Tissue Res*. 2020;379(2):373-387.
34. Kushida N, Fry CH. On the origin of spontaneous activity in the bladder. *BJU Int*. 2016;117(6):982-992.
35. Vahabi B, Santosh B, Chakrabarty B, Fry C. 25 The role of the mucosa in mediating spontaneous contractions of the pig urinary bladder. *Continence*. 2022;2:100215.
36. Robilotto GL, Yang OJ, Alom F, Johnson RD, Mickle AD. Optogenetic urothelial cell stimulation induces bladder contractions and pelvic nerve afferent firing. *Am J Physiol Renal Physiol*. 2023;325(2):F150-F163.
37. McLatchie LM, Young JS, Fry CH. Regulation of ACh release from guinea pig bladder urothelial cells: potential role in bladder filling sensations. *Br J Pharmacol*. 2014;171(14):3394-3403.
38. McLatchie LM, Fry CH. ATP release from freshly isolated guinea-pig bladder urothelial cells: a quantification and study of the mechanisms involved. *BJU Int*. 2015;115(6):987-993.
39. Nishikawa N, Chakrabarty B, Kitney D, Jabr R, Kanai A, Fry C. Stretch- and carbachol-induced ATP release from bladder wall preparations of young and aged mice. *Neurourol Urodyn*. 2020;39(6):1644-1652.
40. Vlaskovska M, Kasakov L, Rong W, et al. P2X3 knock-out mice reveal a major sensory role for urothelially released ATP. *J Neurosci*. 2001;21(15):5670-5677.
41. Birder LA, Nealen ML, Kiss S, et al. β-Adrenoceptor agonists stimulate endothelial nitric oxide synthase in rat urinary bladder urothelial cells. *J Neurosci*. 2002;22(18):8063-8070.
42. Beamon CR, Mazar C, Salkini MW, Phull HS, Comiter CV. The effect of sildenafil citrate on bladder outlet obstruction: a mouse model. *BJU Int*. 2009;104(2):252-256.
43. Zabbarova IV, Ikeda Y, Kozlowski MG, et al. Benign prostatic hyperplasia/obstruction ameliorated using a soluble guanylate cyclase activator. *J Pathol*. 2022;256(4):442-454.
44. Chakrabarty B, Ito H, Ximenes M, et al. Influence of sildenafil on the purinergic components of nerve-mediated

and urothelial ATP release from the bladder of normal and spinal cord injured mice. *Br J Pharmacol*. 2019;176(13): 2227-2237.

45. Okuyama E, Kawatani M, Hashimoto J, Tanimoto K, Hashimoto M, Matsumoto-Miyai K. The nitric oxide-cyclic guanosine monophosphate pathway inhibits the bladder ATP release in response to a physiological or pathological stimulus. *Physiol Rep*. 2021;9(14):e14938.
46. Minagawa T, Aizawa N, Igawa Y, Wyndaele JJ. Inhibitory effects of phosphodiesterase 5 inhibitor, tadalafil, on mechanosensitive bladder afferent nerve activities of the rat, and on acrolein-induced hyperactivity of these nerves. *BJU Int*. 2012;110(6 Pt B):E259-E266.

How to cite this article: Grundy L, Wyndaele JJ, Hashitani H, et al. How does the lower urinary tract contribute to bladder sensation? ICI-RS 2023. *Neurourol Urodyn*. 2023;1-10.
doi:10.1002/nau.25316