

W15: The Ageing Bladder Reconsidered : Urinary Homeostasis from Basket to Casket

Workshop Chair: Phillip Smith, United States
28 August 2018 15:30 - 17:00

Start	End	Topic	Speakers
15:30	15:45	The geriatric bladder: Recapitulation vs resilience	Phillip Smith
15:45	16:05	Bladder Volume Transduction: Origins and Control	Anthony Kanai
16:05	16:25	Sensory Modulation and Homeostasis	Stefan de Wachter
16:25	16:50	Discussion	Phillip Smith Anthony Kanai Stefan de Wachter
16:50	17:00	Summary: Implications for the ageing bladder	Phillip Smith

Aims of Workshop

Urinary disorders are common and morbid in the aged, yet are too often poorly addressed by a bladder pressure/volume-centric paradigm. A systemic approach is needed. This workshop will reconsider urinary control physiology as integrative control providing biologic adaptability to bladder filling and voiding, gained by maturation and progressively compromised in the ageing system. Loss of resilience with ageing increases the likelihood of urinary disorders but does not preclude adaptive performance. We will specifically focus on the basic science and clinical impact of the bladder as an adjustable sensor and actuator in an ageing homeostatic system. Research and clinical impacts will be discussed among the panel and participants.

Learning Objectives

1. Attendees will understand the concept of homeostasis and its application to urinary function.
2. Attendees will be able to describe an adaptive model of neuroendocrine control of bladder response to volume.
3. Attendees will be able to state ways in which ageing can compromise adaptive capabilities, increasing the risks of homeostatic failure.

Learning Outcomes

By gaining more complete knowledge of the molecular, cellular, tissue and systemic bases for loss of urinary adaptability, we envision being able to identify new preventive, evaluative, and therapeutic approaches. The study of ageing offers a relatively high yield in the discovery of physiologic mechanisms underlying homeostatic failure, thus the lessons learned will contribute to improvements in clinical care across the adult age spectrum. Therefore, we have two specific goals for our participants: First, attendees will reconsider urinary dysfunctions as adaptive failures rather than inherent bladder disease. Second, within their areas of basic, translational, or clinical sciences, attendees will be able to imagine new research directions and opportunities contributing to an integrative understanding of urinary control.

Target Audience

Clinicians and scientists interested in the basic science and clinical translation of adaptive urinary control physiology and the impact of ageing.

Advanced/Basic

Advanced

Conditions for Learning

Each speaker will give a brief presentation summarizing the emerging science of the ageing bladder and its adaptive control. Following these presentations, there will be a 30 minute panel/participant interactive discussion about the role of loss of homeostasis as a key characteristic of the ageing bladder. The session will end with a summary statement by the workshop chair.

Suggested Learning before Workshop Attendance

Vaughan CP, Markland AD, Smith PP, Burgio KL, Kuchel GA; Report and Research Agenda of the American Geriatrics Society and National Institute on Aging Bedside-to-Bench Conference on Urinary Incontinence in Older Adults: A Translational Research Agenda for a Complex Geriatric Syndrome. American Geriatrics Society/National Institute on Aging Urinary Incontinence Conference Planning Committee and Faculty. J Am Geriatr Soc. 2018 Apr;66(4):773-782. doi: 10.1111/jgs.15157 PMID: 29205261

Suggested Reading

1. De Wachter SG, Heeringa R, van Koevinge GA, and Gillespie JI. On the nature of bladder sensation: The concept of sensory modulation. Neurourol Urodyn 30: 1220-1226, 2011.
2. Drake MJ, Kanai A, Bijos DA, Ikeda Y, Zabbarova I, Vahabi B, and Fry CH. The potential role of unregulated autonomous bladder micromotions in urinary storage and voiding dysfunction; overactive bladder and detrusor underactivity. BJU Int 119: 22-29, 2017.
3. Eastham JE, and Gillespie JI. The concept of peripheral modulation of bladder sensation. Organogenesis 9: 224-233, 2013.

4. Inouye SK, Studenski S, Tinetti ME, and Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc* 55: 780-791, 2007.
5. Jansson UB, Hanson M, Sillén U, and Hellstrom AL. VOIDING PATTERN AND ACQUISITION OF BLADDER CONTROL FROM BIRTH TO AGE 6 YEARS: A LONGITUDINAL STUDY. *The Journal of Urology* 174: 289-293, 2005.
6. Kanai A, Fry C, Hanna-Mitchell A, Birder L, Zabbarova I, Bijos D, and Ikeda Y. Do we understand any more about bladder interstitial cells?-ICI-RS 2013. *Neurourol Urodyn* 33: 573-576, 2014.
7. Kanai A, Fry C, Ikeda Y, Kullmann FA, Parsons B, and Birder L. Implications for bidirectional signaling between afferent nerves and urothelial cells-ICI-RS 2014. *Neurourol Urodyn* 35: 273-277, 2016.
8. Sillén U. BLADDER FUNCTION IN HEALTHY NEONATES AND ITS DEVELOPMENT DURING INFANCY. *The Journal of Urology* 166: 2376-2381, 2001.
9. Smith PP. Aging and the underactive detrusor: a failure of activity or activation? *Neurourol Urodyn* 29: 408-412, 2010.
10. Vaughan CP, Markland AD, Smith PP, Burgio KL, Kuchel GA; Report and Research Agenda of the American Geriatrics Society and National Institute on Aging Bedside-to-Bench Conference on Urinary Incontinence in Older Adults: A Translational Research Agenda for a Complex Geriatric Syndrome. American Geriatrics Society/National Institute on Aging Urinary Incontinence Conference Planning Committee and Faculty. *J Am Geriatr Soc*. 2018 Apr;66(4):773-782. doi: 10.1111/jgs.15157.

The Geriatric Bladder: Recapitulation vs. Resilience

Phillip Smith

Urinary symptoms and loss of control are increasingly problematic with advancing age, yet current bladder-centric approaches are often limited to compensatory or palliative measures. We propose a new understanding of the ageing bladder. Urinary control should be considered as a manifestation of an adaptive system, integrating afferent activity about bladder volume with other inputs in order to optimize responses to global physiologic challenge. During prenatal development and early postnatal life, available evidence is suggestive of neurologic maturation superimposed on an enlarging lower urinary tract structure. By the time of toilet training, low pressure urine storage in a bladder sufficiently sized to allow uninterrupted sleep, coupled with synergic voiding is expected. Further maturation leads to completed central monitoring and complete control over storage/voiding in early adolescence. Brain control over bladder volume transduction is an integral part of this homeostatic system, analogous to other organ systems. The fully matured system is highly resilient to physiologic stressors throughout much of adult life. In a resilient system, objective function might evolve in later life as homeostatic mechanisms compensate for age- (and disease-) associated component changes. Deviations from “normal” do not preclude *adaptive* function. System success is measured not by objective function rather by freedom from intrusive symptoms. Ageing is associated with global loss of resilience. Gradual component compromise of homeostatic mechanisms with advancing age increases the likelihood of failure to adapt to external and internal physiologic stressors. Impaired cortical control over reflexive voiding leads to disorders of urine storage, and loss of a synergic voiding reflex can contribute to incomplete emptying and intermittent voiding. While the structural aspects of the lower urinary tract in old people remains a continuous evolution of adult life, cognitive impairment and loss of resilience to mounting physiologic challenges lead to a recapitulation of early life storage and voiding patterns.

Bladder Volume Transduction: Origins and Control

Anthony Kanai

This talk will focus on the development of bladder volume regulation and how ageing impacts its control. In infants, before neuronal innervation of the bladder is complete, voiding is reflexive where increasing bladder volume evokes micturition through a bladder-to-spinal cord reflex. With maturation, processing of afferent activity takes place in the pontine micturition center (PMC) in the brainstem which is under voluntary cortical control. However, neonatal bladder reflex can reemerge when communication with the PMC is disrupted as can occur with spinal cord injury. The discussion will cover the general consequences of ageing in the lower urinary tract (LUT) including inflammation and increased oxidative stress that lead to cell damage and further inflammation. This can result in cell proliferation leading to fibrosis and urothelial hyperplasia, and chronically, cell senescence with the loss of functionally including decreased urothelial transmitter release or responsiveness of the sensory nerves in the bladder wall.

Bladder volume and compliance are influenced by mechanical and sensory mechanisms which can augment the response of the bladder to changes in intravesical pressure. In the urothelium, mechanosensitive piezo and transient receptor potential (TRP) ion channels can detect urothelial cell distension in response to increasing luminal volume. Urothelial distension can trigger the release of signalling factors such as ATP that can act on afferent nerves that innervate the mucosa. Mechanosensitive afferents also detect changes in bladder wall tension where their sensitization can decrease the threshold for activation. Conversely, loss of sensation or degeneration due to ageing or neurogenic damage can increase the activation threshold leading to underactive bladder (UAB). Lastly, fibrosis can also enhance the rate of wall tension generation, reducing the volume necessary to achieve threshold pressure thus reducing bladder capacity.

Ageing is associated with increased extracellular matrix collagen deposition, particularly in patients with benign prostatic hyperplasia (BPH). The inflammatory condition combined with bladder fibrosis promotes decreased bladder capacity and increased frequency. Increased detrusor spontaneous contractions due to ageing have been associated with decreased

compliance due to stimulation of afferent nerves in the bladder wall. Conversely, there can also be impairment of intracellular Ca^{2+} handling that can decrease detrusor contractility and contribute to UAB. Ageing, oxidative stress and inflammation have been shown to alter urothelial structure and function. There are reports of increased urothelial transmitter release which could increase afferent nerve stimulation leading to urinary frequency. However, it is also possible that ageing decreases urothelial sensory activity due to cellular senescence to increase the micturition threshold pressure. There are conflicting reports on the effects of ageing on bladder sensory function. Clinically, the LUT symptom most commonly reported is urinary frequency which would imply afferent nerve sensitization. However, decreased sensation is also associated with ageing which could be a contributing cause of UAB.

Sensory modulation and homeostasis

Stefan de Wachter

Voluntary control of the lower urinary tract and adequate sensing of bladder contents are prerequisites to achieve normal continence and voiding. At infancy, this bladder control is achieved with transition of a reflex mediated interrupted voiding to a voluntary synergic voiding after toilet training. During life, bladder control further evolves not only due to changes in the lower urinary structure, but also due to changes in the nervous system and even events in the emotional and cognitive area.

During bladder filling afferent/sensory information is transmitted to different areas in the brain stem where further processing occurs by interaction with different brain areas. This processing plays a key role in establishing correct sensing of bladder content and modulation of it, depending on social circumstances. There appears to be no linear relationship between bladder volume and perception of bladder volume. Although afferent input is closely linked to increasing volumes, perception is also dependent on learned behaviour, memory and cognition. Healthy individuals have the ability to “modulate” bladder sensation to integrate bladder function into daily activities—*e.g.*, we may have increased sensation when we are heading to the toilet, but may suppress these increased sensations if the intention to void is interrupted for example because of closure of the toilet. Loss of the ability to “modulate sensation” may predispose persons to pathology such as overactive bladder or urgency incontinence. Since this control clearly is not only dependent on lower urinary tract function, but also on involvement of different brain areas, ageing can have an impact at the different levels. In this presentation, the different components that may play a role in sensory modulation will be discussed.