Regulation of bladder function: new insights into participants and mechanisms
W9, 15 October 2012 09:00 - 12:00

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**Aims of course/workshop**
This workshop aims to provide an update on new data concerning the regulation of bladder function. We will focus on interstitial cells located in the bladder wall and their relation with nerve fibres and smooth muscle cells. New insights on the properties of the human detrusor will be discussed. We will also address the role played by neurotrophins in the regulation of the bladder function. Finally, we will discuss the impact of these novel insights on the treatment of bladder pathologies, such as overactive bladder syndrome.

**Educational Objectives**
This workshop will provide delegates with an updated insight into the mechanisms that regulate bladder activity at the tissue and organ level. Recent studies have generated exciting new data regarding the role of a recently identified cell population present in the bladder wall; expanded our knowledge of the properties of detrusor smooth muscle cells and augmented our understanding of the modulation of bladder neural control. Delegates will learn how aspects of these new results are already in the process of being translated into the clinic. We anticipate that this workshop will be valuable for those involved in clinical and basic science research as well as health care practitioners.
Regulation of bladder function: new insights into participants and mechanisms

Chair and speaker: Célia D. Cruz, Department of Experimental Biology, Faculty of Medicine and IBMC – Inst. Biologia Celular e Molecular, University of Porto, Portugal

Speakers:
Karen McCloskey, Centre for Cancer Research and Cell Biology, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University, Belfast, United Kingdom
Chris Fry, Institute of Biosciences and Medicine, University of Surrey, United Kingdom
Francisco Cruz, Department of Urology, Faculty of Medicine and Hospital de S. João and IBMC – Inst. Biologia Celular e Molecular, University of Porto, Portugal

General Aims and objectives
This workshop aims to provide an update on the control of bladder function as our grasp of the cellular and molecular mechanisms governing micturition has increased immensely over the years. We will focus on interstitial cells, located in the bladder wall, and their relation with nerve fibres and smooth muscle cells and new insights on the properties of the human detrusor will be discussed. We will also focus the role played by neurotrophins in the regulation of the bladder function. Finally, we will address on basic science findings are being translated into clinics. These are the summaries of each lecture that composes the present workshop.

Bladder interstitial cells: an up-to-date comparison of their distribution and role in normal and dysfunctional bladder
Karen D McCloskey
Bladder contractility has traditionally been ascribed to the nervous system or to the myogenic properties of the detrusor smooth muscle cells (SMC). More recently, it has become clear that other partners, located in the bladder wall, actively interact with nerve fibres and detrusor smooth muscle and act to modulate bladder physiology. One of these partners, the novel interstitial cells (IC) have been studied in bladder for more than a decade and this field of research is dynamic and exciting, advancing our knowledge of cellular communication within the bladder. The current state of the art in bladder IC research will be addressed in this lecture with particular emphasis on:

- The sub-types of IC now known to exist in mucosal and detrusor layers of the bladder wall, their morphological properties, cellular interactions and the panel of markers used in their identification.
- Comparison of the differences in IC distribution in normal and dysfunctional bladders including animal models of spinal cord injury, denervation, diabetes and bladder outlet obstruction.
- Correlation between IC distribution and physiological readouts of bladder activity at the organ level from in vivo cystometry and ex vivo pressure-volume recordings and at the tissue level from e.g. in vitro recordings of contractility.
- The differing physiological properties of IC in the lamina propria and IC in the detrusor with reference to ion channel and receptor expression, electrical activity and calcium signalling. The putative roles of the IC subtypes in normal bladder function will be discussed, with reference to pathophysiology in diseased bladder.
- The emerging area of IC associated with mucosal microvessels in the bladder and their potential role in local control of the microvasculature.
- IC as novel therapeutic targets in the treatment of bladder dysfunction.

**Neural control over muscle function in the bladder wall: what's new?**

**Chris Fry**

The original concept of human bladder contraction regulated by cholinergic nerves has now been augmented by new information regarding the involvement of additional neurotransmitters involved in contractile activation; regional differences of innervation and control in various parts of the bladder; and changes that occur with ageing and associated pathologies. Moreover, contractions result from a hierarchy of central, spinal and local reflexes, and even paracrine interactions between different cell types in the bladder wall. These in turn may be subject to alteration by local prevailing conditions, age and pathology. These levels of complexity will be addressed in this lecture by reference to:

- The significance of different transmitters in contractile activation; the cellular pathways they mediate; their regulation by exogenous factors and conditions and their potential as drug targets.
- Variations in the neural control of contractile activation in the bladder dome, trigone and outflow tract. In particular, the roles of the parasympathetic and sympathetic nervous systems and their potential interaction in regulating contractile activation
- A brief consideration of hierarchical neural control and the consequences of changes that may occur in different pathologies.
- The origin of spontaneous contractions and the influence of tissues overlying the muscle layers. Spontaneous contractions may arise from the musculature itself. In addition
recent work has shown that the mucosa (urothelium and suburothelium) that overlays the detrusor exert powerful effects over contractile performance. The nature of this interaction will be considered.

- The role of the urothelium, suburothelium and detrusor layers in activation of afferent fibres - the pathways whereby afferent activity is regulated and the external factors that initiate such activity will be addressed.
- The association of age and pathology with changes to contractile activation. In particular are age and pathologies, such as detrusor overactivity, separate variables that influence contractile function and what is known about the cellular pathophysiology and age-dependence of contractile changes.

**Neurotrophins in bladder function: possible role in pathological conditions**

Célia Duarte Cruz

Neurotrophins (NTs) are tissue derived trophic factors. Classically, they are viewed as essential proteins that regulate the survival of specific neuronal populations during the embryonic period. In the adult, NTs are known to regulate neuroplasticity events, including peripheral and central sensitization. The family of NTs comprises four members: Nerve Growth Factor (NGF), Brain Derived Neurotrophic Factor (BDNF) and Neutrophins 3 and 4 (NT3 and NT4). NTs exert their effects via their tyrosin-kinase receptors termed Trk, representing high affinity neurotrophin binding sites. In the context of bladder function, NGF is the most well studied NT, with little data available about BDNF and virtually none about NT3 and NT4. In this lecture, the current state of the art regarding the role of NTs in bladder function will be addressed. The highlights will be:

- NGF is produced in the bladder, both in rodents and in Humans. Its exogenous administration induces bladder hyperactivity, irrespective of the route of delivery. The duration of NGF exposure is, however, a crucial factor for NGF-induced bladder dysfunction.
- NGF-driven bladder hyperactivity requires the expression of TRPV1. This indicates that the interaction between the two systems, observed in somatic tissue, is also relevant in visceral hyperactivity.
- Manipulation of NGF, by using antagonists that block binding of this NT to its high affinity receptor or specific scavenging agents, improves bladder function in experimental bladder hyperactivity. However, the therapeutic utility of NGF blocking remains to be fully established.
- BDNF is also produced in the bladder of experimental animals, with no references to the human bladder. Recent studies demonstrate that exogenous BDNF also leads to bladder
hyperactivity. Like with NGF, the duration of BDNF exposure is an important factor for bladder hyperreflexia.

- BDNF seems to exert its downstream effect mostly at the central nervous system. Blocking of downstream signalling events at the spinal cord level effectively reduces bladder hyperactivity.
- Manipulation of BDNF also improves experimental bladder hyperactivity but further studies are warranted to conclude about the potential therapeutic utility of BDNF scavenging.

Has bladder fundamental science already arrived to the clinic? The case of OAB and urinary biomarkers.

Francisco Cruz

Biomarkers are objectively measurable indicators of a biological condition. Recently, urinary nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been investigated as potential biomarkers in the context of overactive bladder (OAB) and this will be the focus of this lecture.

The necessity of a biomarker to assist OAB diagnosis is highly questionable. In fact, OAB is a symptom complex in which urinary urgency must be present in order to establish the diagnosis, once urinary tract infection or other obvious pathology is excluded. Thus, high urinary levels of NGF or BDNF in the absence of urgency cannot establish the diagnosis of OAB.

However, OAB may co-exist with stress urinary incontinence (SUI). Actually, mixed urinary incontinence (MUI) is the most prevalent form of urinary incontinence in elderly women. Clinically, it might be difficult to discriminate OAB wet from SUI, as patients might perceive urgency when urine leaks into the urethra Therefore, a biomarker, able to separate OAB wet from SUI, could be helpful to decide the ideal treatment of difficult cases.

Biomarkers can be useful to phenotype OAB patients. Until now, this aspect has not been evaluated in depth as antimuscarinic treatments were the only approved pharmacologic treatment. However, the emergence of new treatments, including beta3 adrenoreceptor agonists, Botulinum toxin or even PDE5 inhibitors, may call for a marker able to select responders to each treatment.

Biomarkers can also be used to monitor the progression and to predict the prognosis of a disease. OAB is a progressive disease over time. At the moment, the identification of those OAB patients who will progress, persist or remit is still not possible.

The value of a biomarker in medicine also lies in its ability to envisage therapeutic outcome. In OAB, first-line treatment consists in the combination of lifestyle intervention and antimuscarinic drugs. However, it is unclear if treatment should be interrupted upon
symptomatic improvement, or if it should be continued, in order to prevent relapses or progression. Moreover, the ideal moment to start a second-line therapy is, at the moment, totally dependent upon patients’ subjective report of symptoms persistence or worsening. Biomarkers able to identify remissions or refractoriness to particular type of drugs would obviate this problem. It is also uncertain if treatment should be resumed only upon recurrence of bothersome urgency, or if it should be initiated before patients display overt complaints.
Notes
Record your notes from the workshop here