W12: Basic science of the bladder, overactive bladder and mechanistic concepts of pharmacological treatments

Workshop Chair: Russ Chess-Williams, Australia
03 September 2019 11:30 - 13:00

Start	End	Topic	Speakers
11:30	11:35	How the bladder works: muscle, nerves and urothelium	Donna Sellers
11:35	11:40	Mechanisms of bladder overactivity: neurogenic, myogenic, urotheliogenic	Donna Sellers
11:40	11:55	Mechanisms of overactivity: role of infection in refractory overactive bladder	Kylie Mansfield
11:55	12:10	Mechanisms of overactivity: role of inflammation	Michael Winder
12:10	12:25	Benign prostatic hyperplasia and bladder overactivity	Betty Exintaris
12:25	12:40	How current treatments work: all the 3s (M3 and β3), botulinum toxin, resinaferatoxin	Russ Chess-Williams
12:40	12:55	What's on the therapeutic horizon and how these work (PDE5, NSAIDs, antibiotics, ROCK)	Russ Chess-Williams, Kylie Mansfield
12:55	13:00	End of session activity	Russ Chess-Williams, Donna Sellers Betty Exintaris, Kylie Mansfield, Michael Winder

Aims of Workshop

An interactive educational workshop which aims to provide basic training/education in the basic science underpinning our current understanding of the bladder, the overactive bladder, and the current and emerging pharmacological treatments. The workshop will be suitable for a broad audience and is especially aimed at non-science health professionals who would like to refresh and enhance knowledge in the basic science.

Learning Objectives

1. To review the basic science underpinning our current understanding of normal bladder function
2. To review the basic science underpinning our current understanding of bladder dysfunction
3. To understand the mechanism of action of current and emerging pharmacological treatments for bladder dysfunction

Target Audience

Urology, Urogynaecology, Basic Science, Allied Health

Advanced/Basic

Basic

Overview of content

How the bladder works: muscle, nerves and urothelium
Donna Sellers, Basic Scientist, Australia

Normal bladder function is achieved via complex neuronal and non-neuronal mechanisms. This short introduction will briefly overview how the central, autonomic and somatic nervous systems interact in a unique way allowing us to sense bladder filling and evoke urination at the right time and place. The basic cholinergic, adrenergic and non-adrenergic, non-cholinergic (NANC) neurotransmission involved in the motor control of the detrusor and bladder outlet muscles, and the receptor subtypes mediating the contraction/relaxation of the detrusor, urethra and sphincter muscles during the micturition cycle will be reviewed. Additionally, the important role of non-neuronal cells within the urothelium and underlying lamina propria will be introduced, and how these cells actively work together to sense stretch, temperature and numerous chemical signals within the bladder to contribute to normal bladder control.

Mechanisms of bladder overactivity: neurogenic, myogenic, urotheliogenic
Donna Sellers, Basic Scientist, Australia

Whilst still incompletely understood, research on the mechanisms underlying bladder overactivity has been centred on three main theories, with alterations at the neuronal level, at the level of the detrusor smooth muscle and more recently within the urothelium/lamina propria. This section of the workshop will set the scene by overviewing the neurogenic, myogenic and urotheliogenic hypotheses, in which alterations may include damaged central inhibitory neuronal pathways, sensitisation of sensory neuronal pathways, altered properties of the detrusor smooth muscle cells, increased coupling between muscle and interstitial cells, and the increasing evidence for enhanced signalling and release of chemical mediators such as ATP.

Mechanisms of overactivity: role of infection in refractory overactive bladder
Kylie Mansfield, Basic Scientist, Australia

ICS terminology states that urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome. These symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity (DO) and the terms can be used if there is no proven infection or other obvious pathology. However, many patients with OAB report a history of recurrent urinary tract infection. Low-count bacteriuria is now known to be important in women with refractory detrusor overactivity (DO), and at the time of acute exacerbation women with refractory DO have bacteriuria often without the classical symptoms associated with UTI such as acute dysuria. Women with newly diagnosed DO are approximately 6 times more likely to have low count bacteriuria compared to those with a stable bladder. This section of the workshop will further discuss the evidence for a role of infection in the aetiology of OAB, along the findings of our laboratory studies which have been aimed at elucidating the underlying mechanisms. Briefly, the presence of bacteria intracellularly within the urothelial cells from refractory DO patients may lead to the release of cytokines, which recruit white blood cells to infiltrate the area, resulting in further cytokine release and the release of increased amounts of the signalling molecule adenosine triphosphate (ATP). ATP sensitises afferent nerves and thus in excess may lead to increased sensations of urgency and DO. This is supported by the finding of increased ATP in the urodynamic fluid from these patients, which correlated with the first desire to void and symptoms of urgency and may point to a possible pathogenesis for refractory DO.

Mechanisms of overactivity: role of inflammation
Michael Winder, Pharmacologist, Sweden

This section of the workshop will aim to detail the critical role that inflammation plays in the development and maintenance of overactive bladder (OAB). Inflammation of the bladder, or cystitis, is often caused by urinary tract infection but can also arise in the non-infected bladder. Notably, cystitis in all forms is often accompanied by symptoms of overactivity. The reasons for bladder overactivity during cystitis will be discussed herein. Inflammation of the bladder leads to alterations in expression of functionally important receptors and signalling molecules. Among the receptors affected by inflammation are key contributors to bladder contraction such as muscarinic and adrenergic receptors, but also purinergic receptors, which are imperative for regulation of afferent signalling. While levels of acetylcholine and noradrenaline seem to remain stable in most instances of bladder inflammation, alterations can be seen in modulating signalling molecules such as nitric oxide, adenosine triphosphate (ATP) and prostaglandins. The importance of these modulating molecules and their main source, the urothelium, will be discussed. Further, the importance of an intact urothelium will be detailed. It has been shown in various studies that disruption of the urothelium, more specifically the glycosaminoglycan (GAG) layer, plays an important role in the aetiology of OAB. The intact urothelium helps maintain normal bladder function and in its intact state acts as a sensing system for the bladder. When disrupted, underlying parts of the bladder can become exposed to the toxic intravesical environment consisting of urine. This is thought to lead to major alterations in afferent signalling, causing overactivity of the bladder. The main cause of urothelial disruption is inflammation. Urothelial disruption and inflammation in a bacteria-free state are accepted traits of interstitial cystitis/bladder pain syndrome (IC/BPS). This section will highlight the inevitable links between IC/BPS and OAB. This section will also explore possible links between cystitis and prostatitis and the importance of this in the occurrence of bladder overactivity.

Benign prostatic hyperplasia and bladder overactivity
Betty Exintaris, Basic Scientist, Australia

The pathogenesis of benign prostatic hyperplasia (BPH) is associated with both the non-malignant growth of the prostate (static component), and/or increased prostatic smooth muscle tone (dynamic component), which can lead to irritative and obstructive lower urinary tract symptoms (LUTS), as a result of bladder outlet obstruction (BOO). Men with BOO frequently have symptoms of OAB, and although still debatable, clinical data supports the notion that OAB may be a consequence of BOO due to BPH. Treatment options for BPH include surgery or pharmacotherapy, which can be effective in select patients but are associated with a myriad of side effects. A lack of fundamental understanding of the basic physiology of the prostate gland remains a significant barrier to developing new and more effective treatments.

Generation and regulation of prostatic smooth muscle tone: There is abundant information regarding the effects of drugs on electrically field stimulated preparations in a variety of animal and human models, however studies characterising the spontaneous basal contractions of the prostate gland are limited. In a human model of prostate contractility, we reported that prostate smooth muscle tissue exhibits myogenic activity where the smooth muscle cells can contract and relax regardless of neurological input. The function of the smaller myogenic contractions is to continuously mix the prostatic secretions such that they do not stagnate, the larger neurogenic contractions have a significant role in expelling the prostatic secretions during ejaculation. It remains to be seen whether the smaller myogenic contractions provide a better or different drug target to what is currently available.

Brief overview of current therapies: Current pharmacotherapies for LUTS associated with BPH aim to reduce the size or to reduce the smooth muscle tone of the prostate. The size and growth of the prostate gland is driven by androgens and androgen blockade (using 5α-reductase inhibitors) is effective in reducing its size. Smooth muscle tone and contractility is treated using

adrenoceptor α-antagonists. Interestingly, in the presence of a variety of α1-antagonists, there is a significant reduction in nerve or agonist-evoked prostatic smooth muscle contractility, which formed the premise for using these agents in clinical practice. Overall, current pharmacotherapies do not work in all patients, and can still result in debilitating side effects.

Overview of emerging pharmacotherapies: Emerging or novel pharmacotherapies for LUTS, secondary to BPH reduce smooth muscle tone by prolonging the effect of nitric oxide (phosphodiesterase type 5 (PDE5) inhibitors), blocking Ca^{2+} channels (dihydropyridines) or reducing inflammatory mediators (cyclo-oxygenase (COX) inhibitors). The exciting aspect is that these drugs are already on the market to treat erectile dysfunction, hypertension and inflammation, respectively.

Understanding the basic physiology of the prostate gland will consequently lead to a better understanding of the aetiology of BPH and the development of better pharmacotherapies to manage LUTS associated with BPH, particularly in men with comorbidities. The potential to use these drugs in combination with lower doses of 'uroselective' α1 antagonists, such tamsulosin, may prove a better strategy than current treatment regimens using monotherapy, thereby improving the quality of life for patients.

How current treatments work: all the 3s (M3 and β3), botulinum toxin, resinaferatoxin
Russ Chess-Williams, Pharmacologist, Australia

Currently the main treatments for overactive bladder are the muscarinic receptor antagonists and beta-adrenoceptor agonists. This section will discuss the rationale behind the development of these agents. Both were developed with the intention of depressing detrusor smooth muscle contraction by either blocking the actions of acetylcholine on detrusor M3 receptors or by depressing detrusor contractility via beta3-adrenoceptor stimulation. In reality the actions of these drugs may be far more complex with muscarinic receptors located not only on the detrusor but also on the urothelium, interstitial cells, sensory nerves and motor nerves. All of these sites may be targets for drug action. Similarly, for beta-receptors, these are not located solely on the detrusor muscle and the actions of these drugs may be more complex than originally thought. The mechanisms of action of other therapies that have been suggested for overactive bladder will also be considered, including capsaicin/resinaferotoxin and botulinum toxin.

What's on the therapeutic horizon and how these work (PDE5, NSAIDs, antibiotics, ROCK)
Russ Chess-Williams, Kylie Mansfield

This final section will take a brief look at what treatments may be on the horizon. When the role of infections in overactive bladder has been elucidated, antibiotic treatments may be a major treatment option for some patients. For others, treatments such as inhibitors of phosphodiesterase enzymes or alpha1-adrenocptor antagonists may be of use. The mechanism of action of these agents will be discussed. Another emerging mechanism of controlling detrusor activity is the "calcium sensitisation" pathway. Traditionally we think of rises in intracellular calcium causing smooth muscle contraction, but another intracellular pathway, the rho kinase pathway, is also involved in regulating detrusor responses and could be a target for drug development, if selectivity for the detrusor can be established. Each of these potential drug mechanisms will be discussed.

End of session activity
A brief activity to check learning, attendees will be provided with a worksheet.