### 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-adrenoceptor 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.
Workshop 12
Basic science of the bladder, overactive bladder and mechanistic concepts of pharmacological treatments

Chair: Prof. Russ Chess-Williams
Centre for Urology Research, Bond University, QLD

Workshop speakers

Dr Donna Sellers
Bond University
Dr Betty Exintaris
Monash University
Dr Kylie Mansfield
University of Wollongong
Dr Michael Winder
University of Gothenburg

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Institution (non-industry) funded
Sponsored by: Bond University

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Institution (non-industry) funded
Sponsored by: University of Wollongong

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Self-funded
Institution (non-industry) funded
Sponsored by: University of Gothenburg

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation.
### Betty Exintaris

#### Affiliations to disclose†:

| None |

#### Funding for speaker to attend:

- **Self-funded**
- **Institution (non-industry) funded**
- **Sponsored by:** Monash University

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

- Handout for all workshops is available via the ICS app, USB stick and website.
- Please silence all mobile phones
- PDF versions of the slides (where approved) will be made available after the meeting via the ICS website so please keep taking photos and video to a minimum.

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| Objectives of the session |

#### Basic science of the bladder and overactive bladder
1. How the bladder works: muscle, nerves and urothelium
2. Mechanisms of bladder overactivity: neurogenic, myogenic, urotheliogenic
3. Mechanisms of overactivity: role of infection in refractory overactive bladder
4. Mechanisms of overactivity: role of inflammation
5. Mechanism of overactivity: benign prostatic hyperplasia and bladder overactivity

#### Mechanistic concepts of pharmacological treatments
6. How current pharmacological treatments work: all the 3’s (Anti-muscarinics (M3) and β3-adrenoceptor agonists)
7. What’s on the therapeutic horizon and how these work (botox, RTX, PDE5 inhibitors)

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| The science of the bladder and overactive bladder |

#### 1. How the bladder works

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| Bladder anatomy

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| The science of the bladder and overactive bladder |

#### 1. How the bladder works

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| Bladder anatomy

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| Bladder anatomy

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| Bladder anatomy

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Nervous control of the bladder

Regulation is via complex neural control systems:

Central Nervous System (Voluntary)
- Cerebral cortex
- Brain stem
- Spinal cord

Peripheral nerves
- Somatic nerves
- Autonomic Nervous System (Involuntary)

Efferent motor nerves control the detrusor & urethra

ATP
NO
P2X1 receptor


Neurotransmission – storage phase

1. Contraction of detrusor muscle by increased parasympathetic signals
2. Opening of internal urethral sphincter by decreased sympathetic signals
3. Voluntary opening of external urethral sphincter by somatic nervous system

Role of non-neuronal cells

The urothelium/ lamina propria – ‘sensory web’

Important in normal bladder function/dysfunction & a target of drug treatments
2. Mechanisms of bladder overactivity

Overactive Bladder (OAB or OABS) – a symptom-defined condition
- Characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence, in the absence of a urinary tract infection or other obvious pathology


Prevalence of OAB

- Overactive bladder & urinary incontinence affect >500 million people worldwide
- OAB affects an estimated 17% of adults over the age of 40
- Prevalence increases markedly with age >30% beyond 65yrs
- Associated with a number of chronic conditions including diabetes, multiple sclerosis, dementia

Pathophysiology of OAB & DO

Types of OAB
- Neurogenic OAB/DO
- Bladder Outlet Obstruction – BPH
- Idiopathic – unknown cause

The pathophysiology is complex, and likely to be patient specific & multifactorial

Neurogenic OAB & DO

- Damaged central inhibitory neural pathways
- Sensitisation of sensory nerves
- Unmask primitive voiding reflexes
- Triggers overactive detrusor contractions

Urothelial dysfunction/sensory OAB

- Increased signalling from the urothelium/lamina propria

25/09/2019
3. Mechanisms of bladder overactivity

A role for infection in overactive bladder?

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. These terms can be used if there is no proven infection or other obvious pathology.

However many patients with OAB report a history of recurrent UTI.

1. “Low-count” bacteriuria now known to be important in women with refractory DO
2. At time of acute exacerbation women with refractory DO have bacteriuria rates of 39% of MSUs, 56% of patients 27% of CSUs, 28% of patients often without the classical symptoms associated with UTI such as acute dysuria
3. Newly diagnosed DO are approximately 6 times more likely to have low count bacteriuria compared to those with a stable bladder

Detection of intracellular bacteria in urge incontinence

To test for the presence of intracellular bacteria in the urine of patients with detrusor overactivity or mixed incontinence +/- a history of UTI, and compare this to a control group of patients with no history of infection.
Wright staining of urothelial cells

<table>
<thead>
<tr>
<th>Pure DO</th>
<th>Mixed incontinence +/- UTI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth on routine media</td>
<td>11%</td>
<td>27%</td>
</tr>
<tr>
<td>Bacteria seen on Wright staining</td>
<td>75%</td>
<td>55%</td>
</tr>
</tbody>
</table>
Results

➢ 3 Class of cytokines:
   ➢ Pro-inflammatory
   ➢ Chemokines
   ➢ Regulatory (Anti-inflammatory)

Results:

➢ 4 (of 27) cytokines were increased in refractory DO patients compared to controls
➢ 17 (of 27) cytokines were different in refractory DO patients with UTI

<table>
<thead>
<tr>
<th>Cytokine / Chemokine</th>
<th>Control vs RDO NG</th>
<th>Control vs RDO UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-inflammatory Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>ns</td>
<td>0.023</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>ns</td>
<td>0.038</td>
</tr>
<tr>
<td>IL-2</td>
<td>ns</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-7</td>
<td>ns</td>
<td>0.007</td>
</tr>
<tr>
<td>IL-12p</td>
<td>70</td>
<td>0.003</td>
</tr>
<tr>
<td>IL-17A</td>
<td>0.025</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNF-α</td>
<td>ns</td>
<td>0.004</td>
</tr>
<tr>
<td>Basic FGF</td>
<td>ns</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Chemokines

<table>
<thead>
<tr>
<th>Cytokine / Chemokine</th>
<th>Control vs RDO NG</th>
<th>Control vs RDO UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>ns</td>
<td>0.006</td>
</tr>
<tr>
<td>IP-10</td>
<td>ns</td>
<td>0.001</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>ns</td>
<td>0.040</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>G-CSF</td>
<td>ns</td>
<td>0.027</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.0005</td>
<td>0.048</td>
</tr>
<tr>
<td>RANTES</td>
<td>ns</td>
<td>0.034</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>ns</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Regulatory Cytokines

<table>
<thead>
<tr>
<th>Cytokine / Chemokine</th>
<th>Control vs RDO NG</th>
<th>Control vs RDO UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>ns</td>
<td>0.008</td>
</tr>
<tr>
<td>IL-5</td>
<td>0.016</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-6</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>IL-13</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Possible pathogenesis of refractory DO??

Cytokines

ATP → Cytokines → white blood cell infiltration → more cytokines and ATP release → sensitisation of efferent nerves → sensation of urgency and DO

Mechanisms of bladder overactivity

Role of inflammation

4. Mechanisms of bladder overactivity

Role of inflammation

IC/BPS – a chronic condition

ICS: Persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as an urgent need to void or urinary frequency

Classic IC/BPS vs non-classic IC/BPS

Classic IC/BPS is associated with disruption of the GAG layer, disruption of the urothelium, increased expression of nitric oxide (NO) and Hunner lesions (5-50%)

Characteristics of non-bacterial cystitis – mostly shared with classic IC/BPS

• Detrusor overactivity/aferent sensitisation
• Disruption/proliferation of the urothelium
• Up-regulation of cytokines, ATP & NO
• Macroscopical signs of inflammation

Cystitis

Bacterial (UTI – most common) or non-bacterial

Classic symptoms:
• Stinging/burning during micturition
• Urgency
• Frequency
• Lower abdomen pain

IC/BPS vs non-bacterial cystitis

Classic IC/BPS vs non-classic IC/BPS

Classic IC/BPS is associated with disruption of the GAG layer, disruption of the urothelium, increased expression of nitric oxide (NO) and Hunner lesions (5-50%)
**Symptoms of OAB upon induction of inflammation**

<table>
<thead>
<tr>
<th>Index</th>
<th>CYP-treated group</th>
<th>Control group</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC score</td>
<td>5.5 ± 2.3</td>
<td>3.0 ± 1.7</td>
<td>-0.01</td>
</tr>
<tr>
<td>IPSS</td>
<td>40 ± 6.3</td>
<td>64 ± 2.5</td>
<td>-0.09</td>
</tr>
<tr>
<td>ICI</td>
<td>0.9 ± 0.16</td>
<td>1.3 ± 0.22</td>
<td>-0.01</td>
</tr>
<tr>
<td>ITS</td>
<td>2.6 ± 0.1</td>
<td>3.5 ± 0.2</td>
<td>-0.04</td>
</tr>
<tr>
<td>VAS</td>
<td>10 ± 2.5</td>
<td>9.0 ± 3.0</td>
<td>-0.08</td>
</tr>
<tr>
<td>NC (mean/d)</td>
<td>0.37/0.27</td>
<td>0.34/0.25</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

**Disruption of the urothelium**

The urothelium is a sensing system – thermal, mechanical, chemical

Glycosaminoglycan (GAG) layer disruption → afferent nerve activation + signalling molecule alterations + spontaneous electrical activity

→ Logical interest in treatment targeting the urothelium, nonetheleast intravesical treatment

**Ranking the possible links between cystitis/IC and OAB**

1. Urotheliogenic
2. Myogenic
3. Neurogenic

**Autonomic signalling**

ACh → muscarinic rec
A/NA → adrenergic rec
Modulators
Nitric oxide, ATP, cytokines, prostaglandins, substance P, PACAP/VIP
All up-regulated during cystitis

**Increased stretch-induced release of ATP in patients with IC/BPS**

- Sun et al, 2001
- Quantified ATP in the urine of healthy and IC patients - more than twice as high
- Main source: the urothelium

**ATP sensitises/activates afferent nerves**

↑ ATP (urothelium) → ↑ afferent signalling → ↑ sensation of urgency → ↑ frequency (most often)
ATP-induced overactivity

P2X2/3 – afferent neurons, detrusor & urothelium

Elevated nitric oxide in the urinary bladder in all forms of cystitis

• Lundberg et al, 1996
• Measured NO directly in the urinary bladder in patients with infectious cystitis, interstitial cystitis, irradiation cystitis, and cystitis induced by antitumor treatment with bacillus Calmette-Guérin
• NO levels were 30 to 50 times higher in all varieties of cystitis as compared to controls

Nitric oxide affects bladder contractility

Nitric oxide – regulation of inflammation

Absence of L-NAME
Presence of L-NAME


Nitric oxide – regulation of inflammation

Interactions between inducible nitric oxide synthase and cyclooxygenase-2 in response to ischemia-reperfusion of rabbit bladder, BJUI 2009 (106) 716-722

Figure adapted from de Oliveira et al (2016) Activation of soluble guanylyl cyclase by BAY 58-2667 improves bladder function in cyclophosphamide-induced cystitis in mice, Am J Physiol Renal Physiol 2016 Jul 1; 311: 85-93

Should standard OAB treatment include antiinflammatory drugs?

Keeping it simple: there is a clear link between bladder inflammation and OAB/DO

Multiple reports show benefit of anti-inflammatory treatment, usually decreasing ATP or NO or both

Conclusion: Yes? if the right patients are being treated

Questions/workbook (5 mins)
5. Mechanisms of bladder overactivity

BPH & OAB

The prostate

- Walnut sized, sponge-like gland located at the base of the bladder
- Indirectly affects fertilisation (increases sperm motility, provides nourishment)
- Columnar epithelial cells produce secretions (stored in the prostatic ducts)
- Prostatic fluid expelled upon ejaculation (autonomic control)
- Prostatic fluid, together with the fluid expelled from the seminal vesicle makes up the bulk of semen in which sperm is suspended to make up the ejaculate.
- Prone to disease in older men

BPH

- Non-malignant enlargement of the prostate
- Extremely prevalent in older men
  - ~60% of men by the age of 60
  - ~80% of men by the age of 80
- Arises in the Transition Zone

Adapted from Green et al. Campbell's Textbook of Urology. 2015

BPH is a common disease of ageing men

However, the severity of symptoms does not correlate to the size of the prostate

Summary

Link between OAB and BPH

BPH is a common disease of ageing men

- Non-malignant enlargement of the prostate
- Extremely prevalent in older men
  - ~60% of men by the age of 60
  - ~80% of men by the age of 80
- Arises in the Transition Zone

Adapted from Green et al. Campbell's Textbook of Urology. 2015
Life cycle of the prostate

L.U.T.S.
- hesitancy
- reduced stream
- dribbling
- straining
- nocturia
- frequency
- urgency

The aetiology of BPH is complex and poorly understood

Benign Prostatic Hyperplasia
- Proliferation of tissue (static component)
- Increased muscle tone (dynamic component)

Treatment
- Surgery
- Pharmacotherapy

5α reductase inhibitors (finasteride, dutasteride)
- target static component
- inhibit the proliferative action of androgens
- improve symptoms and urinary flow rate, also reduce prostate size and rates of acute urinary retention and surgery
- may take 6 months of treatment before symptoms improve (full effect after 12–18 months)
- sexual side effects including impotence, decreased libido and abnormal ejaculation.

Selective alpha blockers (α1 adrenoceptor antagonists)
(tamsulosin, alfuzosin, silodosin)
- target dynamic component
- decrease the smooth muscle tone by blocking prostatic α1-adrenoceptors
- most effective, fastest acting (can improve symptoms within 48 hours - full effect in 4–6 weeks)
- can also improve urinary flow rates
- they appear to be effective regardless of prostate size
- can be associated with postural hypotension and possible ejaculatory effects.

Combination therapy
- decrease the smooth muscle tone by blocking prostatic α1-adrenoceptors thus relieving urethral obstruction
- inhibit the proliferative action of androgens
- consider combination treatment when prostate >30–40 cm3 and rapid relief of troublesome symptoms is required.
Other pharmacotherapy
- Tadalafil
- Mirabegron

Age Related Differences in Responsiveness to Sildenafil and Tamsulosin are due to Myogenic Smooth Muscle Tone in the Human Prostate.

6. Mechanistic concepts of pharmacological treatments

How current treatments work: all the 3’s

Goal of drug treatment is to decrease detrusor activity and increase bladder capacity

Two main classes of treatment available:
- Anti-cholinergics (muscarinic receptor antagonists)
- Beta-3-adrenoceptor agonists

Adverse effects of anti-muscarinics

- Iris: Blurred vision
- Salivary Glands: Dry mouth
- Heart: Tachycardia
- Stomach & oesophagus: Dyspepsia
- Colon: Constipation
- CNS: Dizziness, impaired memory & cognition

Development of muscarinic antagonists for OAB

Drug M3 selectivity
- Tolterodine – non-selective
- Oxybutynin – 3-fold selective
- Darifenacin – 10-fold selective
- Solifenacin – 30-fold selective

M3 receptors
- Bladder (therapeutic effect)
- Salivary gland (dry mouth)
- GI tract (constipation)
Mechanism of action in OAB

They block the actions of Ach after released from parasympathetic nerves ... No!

In theory, if muscarinic antagonists only did what they were developed to do (ie. stop Ach from nerves stimulating the detrusor) they should not work in detrusor overactivity.

WHY NOT?
Detrusor overactivity is a problem during the filling stage of the micturition cycle (when nerves not releasing Ach).

SO HOW DO THEY WORK?

Other sites of action for anti-muscarinics?

Mechanism of action in OAB

How β3-adrenoceptor agonists work

Relaxes the bladder muscle

Adverse effects of β3 agonists

Limited distribution of β3-receptors
Few adverse effects

Options beyond oral treatments

Botulinum toxin

• Injected intravesically into bladder wall

Mechanism of action:
• Prevents release of Ach from nerves
• Prevents release of ATP from the urothelium
Other potential treatments for OAB

**Vanilloids**

- Intravesical administration into bladder lumen
  - Capsaicin*
  - Resiniferatoxin*

**Mechanism of action:**
- Deplete sensory nerves of neurotransmitters

7. What's on the therapeutic horizon?

Other potential treatments for OAB

**α₁-adrenoceptor antagonist**

- OAB associated with bladder outlet obstruction and enlarged prostate
  - Tamsulosin

- *indicated for BPH

TURP

**Mechanism of action:**
- No α₁-receptors in detrusor
- Inhibit sensory signalling in spinal cord

Phosphodiesterase inhibitors

- e.g. Tadalafil#
- LUTS/OAB associated with erectile dysfunction
- OAB in women

- *indicated for moderate to severe LUTS associated with BPH

Mechanism of action:
- Inhibition of detrusor
- Other actions?

Anti-inflammatories and OAB

**Effect of indomethacin (NSAID) treatment on OAB symptoms**

Two small studies conducted in the early 1980's

1. 6 weeks of indomethacin treatment (48 patients): 17% of patients showed improvement in OAB symptoms (urgency, frequency, urge incontinence and nocturia) following 6 weeks with indomethacin [Delaere et al., 1981]

2. 4 weeks of indomethacin treatment (32 patients): Improvement in urgency ↓9%, frequency ↓29%, urge incontinence ↓19% and nocturia ↓29% [Cardozo and Stanton, 1980]

Antibiotics and OAB

**OAB symptoms at baseline and after 6 weeks of antibiotic therapy**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 6 week course of antibiotics</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Frequency</td>
<td>12.8 ± 3.5</td>
<td>8.7 ± 2.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Nocturia</td>
<td>2.0 (1.0-3.0)</td>
<td>1.0 (0.0-3.0)</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>PPRC Scores</td>
<td>5.0 (4.0-6.0)</td>
<td>2.0 (1.0-4.0)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PPUS Scores</td>
<td>3.0 (1.0-5.0)</td>
<td>2.0 (1.0-5.0)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Significant improvement in symptom scores but not placebo controlled

PPRC Patients’ Perception of Bladder condition
PPUS Patients’ Perception of Intensity of Urgency Scale
**RCT of antibiotics**

Phase IIb RCT of antibiotic therapy vs placebo at St George Hospital + Wollongong
Women with urodynamically proven refractory DO
2:1 ratio of antibiotics versus placebo (with darifenacin in both groups)
6 weeks of rotating antibiotics (2 weeks each)
- Augmentin Duo (or trimethoprim)
- Norfloxacin
- Nitrofurantoin

All patients will be followed for 6 months

Results are being presented at ICS (session 8, Wednesday pm)

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**Summary of drug actions**

The actions of M3 antagonists and β3 agonists are not limited to the detrusor

Additional actions:
- Urothelium
- Sensory nerves
- Efferent nerves
- Interstitial cells

New therapies targets include:
- Antibiotics
- Anti-inflammatories
- Second messenger systems (cAMP/cGMP)
- Sensory system (capsaicin/RTX)

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Thank you for attending!