W37: PDE5 Inhibitors and Novel Soluble Guanylate Cyclase Activators in the Treatment of Lower Urinary Tract Symptoms—Clinical Implications and Mechanistic Concepts

Workshop Chair: Anthony Kanai, United States
06 September 2019 11:30 - 13:00

Start	End	Topic	Speakers
11:30	11:50	Clinical Relevance of PDE5 Inhibitors and Novel sGC Activators	Marcus Drake
11:50	12:10	Effects of PDE5 Inhibitors and sGC Activators on the Urothelium	Lori Birder
12:10	12:30	Effects of PDE5 Inhibitors and sGC Activators on Sensitised Bladder Afferent Nerves	Anthony Kanai
12:30	12:50	PDE5 Inhibitors, sGC Activators and Bladder Wall Relaxation	Christopher Fry
12:50	13:00	Discussion	All Speakers

Please note that where authorized by the speakers, PowerPoint slides presented at the workshop will be made available after the meeting *via* the ICS website www.ics.org/2019/programme. Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

PDE5 inhibitors (e.g., tadalafil, sildenafil) may be used to treat lower urinary tract symptoms (LUTS). They are proposed to work by increasing protein kinase G (PKG) signalling *via* nitric oxide (NO•)-induced activation of soluble guanylate cyclase (sGC). This alters the functional behaviour of targets including: urothelial cells, afferent and efferent nerves, as well as detrusor smooth muscle, by mechanisms incompletely understood. sGC activators (*e.g.*, BAY-582667) also increase PKG activity but, crucially, can do so in the absence of NO• which can occur if nitrergic nerves are damaged. Our aims are to discuss the cellular targets, mechanisms of actions and therapeutic relevance of PDE5 inhibitors and sGC activators to treat LUTS.

Learning Objectives

i) Provide up-to-date information on the clinical relevance of PDE5 inhibitors and sGC activators for the treatment of LUTS. As BAY-582667 has passed phase 1 safety trials for non-urological pathologies, sGC activators have high translational/clinical relevance for patients with LUTS who are unresponsive to PDE5 inhibitors.

ii) Discuss the putative mechanisms of actions by which PDE5 inhibitors and sGC activators treat LUTS including: i) decreasing urothelial stretch-induced ATP release; ii) dampening sensitised afferent nerve firing rates; and iii) relaxing detrusor smooth muscle.

iii) After the course, attendees will have the latest clinical and scientific information on the use of PDE5 inhibitors and sGC activators in treating LUTS. The information could be applied to attendees' research programs or patient management strategies.

Learning Outcomes

After the course, attendees will have the latest clinical and scientific information on the use of PDE5 inhibitors and the newer sGC activators in treating lower urinary tract dysfunction and relevant models to test these agents. The information could be applied to attendees' research programs or patient management strategies.

Target Audience

Urologists, urogynaecologists, basic scientists and other healthcare workers.

Advanced/Basic

Advanced

Conditions for Learning

None, this is not a hands on course.

Suggested Learning before Workshop Attendance

1) Latest Evidence on the Use of Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia, Gacci et al., Eur Urol., 70:124-133, 2016. PMID: 26806655.

2) PDE5 inhibitors - pharmacology and clinical applications 20 years after sildenafil discovery. Andersson KE. Br J Pharmacol., 175:2554-2565, 2018. PMID: 29667180.

3) Stimulators and activators of soluble guanylate cyclase for urogenital disorders. Mónica F and Antunes E, Nat Rev Urol., 15:42-54, 2018. PMID: 29133940.

Other Supporting Documents, Teaching Tools, Patient Education *etc.* - This handout

This workshop will provide health-care practitioners and scientists with the latest investigational approaches, mechanistic concepts and clinical relevance for using PDE5 inhibitors *versus* the new sGC activators to treat LUTS. We will discuss the pathophysiological mechanisms and therapeutic potentials for PDE5 inhibitors and sGC activators for overactive bladder (OAB) and neurogenic bladder dysfunction (NBD). We will explore the potential advantage of using sGC activators, to work independently of NO• production and how this may remove a particular limitation of PDE5 inhibitors which render them clinically

ineffective where there is nitrergic nerve damage as commonly occurs in NBD. We will demonstrate the clinically relevant effects of PDE5 inhibitors and sGC activators on LUT pathologies using animal models of conditions such as spinal cord injury or artificially-induced cystitis and relate these to patient conditions wherever possible. Experimental approaches will include evaluation of these agents on: urodynamic and cystometric measurements; afferent nerve recordings; urothelial barrier and secretory functions; and bladder wall contractile properties. It is anticipated that these new approaches and concepts will be valuable in facilitating further basic science and clinical research, as well as guiding the clinical management of LUT pathologies. By providing information on groundbreaking research, this workshop aims to increase our ability to provide better world-class health care for urologic patients.

The opening talk will discuss the clinical relevance of PDE5 inhibitors and newer sGC activators to treat LUTS due to BPH and neurogenic injury. The second presentation will provide the latest information on the role of NO• and its receptor, sGC, in urothelial signalling. The third talk will present data on the role of PDE5 inhibitors and sGC activators in modulating afferent nerve sensitisation with the aim to ameliorate OAB/NBD symptoms and improve bladder storage function. The final presentation will discuss the mechanisms of PDE5 inhibitors/sGC activators in promoting bladder smooth muscle relaxation and improving compliance. None of the speakers will present any products or have any conflicts of interest.

Clinical Relevance of PDE5 Inhibitors and Novel sGC Activators
Marcus Drake

The clinical efficacy of PDE5 inhibitors in ameliorating LUTS due to BPH has been reported in multiple trials since 2002, resulting in licensing of tadalafil (5 mg daily) for the treatment of LUTS with or without erectile dysfunction. The most notable effects of PDE5 inhibitors are in decreasing the international prostate symptom scores (IPSS) and improving the quality of life scores without significant effects on maximum flow rates (Qmax). Thus, combining a PDE5 inhibitor with an α1-antagonist (*e.g.,* Tamsulosin) may offer enhanced therapeutic benefits. The PDE5 inhibitor may also mediate relaxation of detrusor smooth muscle and inhibition of sensory nerves to ameliorate LUTS. Small molecule sGC activators such as BAY 58-2667 (Cinaciguat) can induce cGMP production in the absence of nitric oxide or when sGC is inactivated (*e.g.* oxidative stress). Thus, these drugs may be effective in patients refractory to PDE5 inhibitors due to degeneration of nitrergic nerves or inactivation of sGC.

Effects of PDE5 Inhibitors and sGC Activators on the Urothelium
Lori Birder

Urothelial cells in humans and rodents express sGC and produce NO• in response to a number of stimuli including stretch and adrenergic agonists. Bladder stretch also releases ATP, which is limited by the PDE5 inhibitor, sildenafil[4]. As ATP can stimulate $P2X_{2/3}$ receptors on afferent nerves to release neuropeptides which, in turn, can stimulate smooth muscle, NO• may modulate bladder overactivity. Oxidative stress induced inactivation of sGC that may contribute to detrusor overactivity which would be refractory to PDE5 inhibitors but may be treatable with sGC activators.

4) Chakrabarty B, Ito H, Ximenes M, Nishikawa N, Vahabi B, Kanai AJ, Pickering AE, Drake MJ, Fry CH: 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, Epub ahead of print. PMID: 30924527.

Effects of PDE5 Inhibitors and sGC Activators on Sensitised Bladder Afferent Nerves
Anthony Kanai

NO• activates sGC by binding to the heme group on its β-subunit, causing activation of a catalytic domain that converts GTP to cGMP. A prerequisite to this reaction is reduced heme (Fe^{2+}) as NO• does not bind to oxidized heme (Fe^{3+}), and NO•-mediated cGMP production is abolished when heme oxidation is accelerated due to oxidative stress. NADPH cytochrome b5 reductase 3 (Cyb5R3) is a key enzyme in maintaining the sGC heme in the reduced state, however, it can be downregulated by oxidative stress. sGC activators do not require NO• and may act on sGC with an oxidized heme or in its absence, making activators uniquely suitable therapies in pathology. *Ex vivo* bladder afferent nerve recordings from control mice show that bladder stretch evokes afferent firing that is increased in the presence of the sGC inhibitor, ODQ, suggesting that under normal conditions NO• has an inhibitory effect on afferent activity. The PDE5 inhibitor, sildenafil, decreased the firing rate in response to stretch which supports the therapeutic potential of NO•-sGC pathway modulation in treating NDO. Studies further suggest that the mechanisms of action include PKG-mediated inhibition of N-type Ca^{2+} channels and removal of neurokinin-2 (NK_2) mediated inhibition of voltage-gated K^+ channels, both of which hyperpolarize the nerve terminals to reduce afferent firing. We hypothesize that in pathology, degeneration of nitrergic nerves and/or downregulation of Cyb5R3 account for afferent sensitization that is refractory to PDE5 inhibitors but treatable with sGC activators.

PDE5 Inhibitors, sGC Activators and Bladder Wall Relaxation
Christopher Fry

Reports on NO• signalling in the bladder have been varied. Earlier studies in muscle strips indicated that sGC in the bladder neck and proximal urethra is responsible for their NO•-mediated relaxation, while detrusor smooth muscle relaxes in response to β_3-

adrenergic receptor stimulation (β_2 in mice) mediated by cAMP-PKA which promotes cross-bridge dissociation. However, sGC levels in the detrusor of mice are nearly one-half of that expressed in the bladder neck and nearly equivalent to levels in the mucosa. Moreover, it has been demonstrated that sGC expression and cGMP production in aortic rings could be reduced by 90% and still evoke a NO•-mediated relaxation equivalent to controls[5], suggesting that sGC levels in the bladder wall may be sufficient to contribute to relaxation of the detrusor which is supported by preliminary data in mice to be presented.

5). Groneberg, D., Konig, P., Wirth, A., Offermanns, S., Koesling, D., Friebe, A.: Smooth muscle-specific deletion of nitric oxide-sensitive guanylyl cyclase is sufficient to induce hypertension in mice. Circulation, 121: 401, 2010. PMID: 20065162.