W41: The Use of Novel Soluble Guanylate Cyclase Activators to Treat Benign Prostatic Hyperplasia, Obstruction and Fibrosis - Mechanistic Concepts and Clinical Implications

Workshop Chair: Anthony Kanai, United States

Start	End	Topic	Speakers
		Current Pharmacological Options for Treating BPH/BOO and LUTS	Karl-Erik Andersson
		Activators Overcome Nitrergic Nerve Damage and sGC Inactivation to Treat BPH/BOO	Anthony Kanai
		sGC Activators Dampen Sensitized Afferent Nerves, Reverse Fibrosis and Treat LUTS	Lori Birder
		cGMP-dependent Pathways and Smooth Muscle Contraction	Christopher Fry
		Questions	All

Aims of Workshop

BPH can result in bladder outflow obstruction and development of LUTS, and by 80 yrs of age is present in about 75% of men. Pharmacological therapies include alpha-adrenoceptor antagonists, 5-alpha reductase inhibitors, and the PDE5 inhibitor, tadalafil. The efficacy of tadalafil suggests a role for nitric oxide (NO•) through activation of soluble guanylate cyclase (sGC) and production of cGMP - a smooth muscle relaxant, but also an antifibrotic agent. However, patients can become refractory to tadalafil due to nitrergic nerve damage, or sGC inactivation from oxidative stress. We will discuss how sGC activators augment cGMP production under conditions when the NO• pathway is compromised to manage BPH, LUTS and fibrotic development.

Learning Objectives

Provide up-to-date information on the clinical use of PDE5 inhibitors and the therapeutic potential of a novel sGC activator, BAY 58-2667 (cinaciguat), to treat BPH/BOO and associated LUTS. Cinaciguat has passed phase-1 safety trials for non-urological pathologies and has high clinical relevance for patients with BPH/BOO/LUTS, who are unresponsive to PDE5 inhibitors.

Target Audience

Urology, Basic Science

Advanced/Basic

Advanced

Suggested Learning before Workshop Attendance

1. Macoska J, Uchtmann K, Leverson G, McVary K, Ricke W. Prostate transition zone fibrosis is associated with clinical progression in the MTOPS study. J Urol, 202:1240, 2019.
2. Gacci M., Andersson K-E, Chapple C, Maggi M, Mirone V, Oelke M, Porst H, Roehrborn C, Stief C, Giuliano F. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol, 70:124, 2016.
3. Constantinou C. Influence of hormone treatment on prostate growth and micturition characteristics of the rat. Prostate, 29:30, 1996.
4. Zhou Y, Xiao X, Chen L, Yang R, Shi J, Du X, Klocker H, Park I, Lee C, Zhang J. Proliferation and phenotypic changes of stromal cells in response to varying estrogen/androgen levels in castrated rats. Asian J Androl, 11:451, 2009.
5. Li J, Wang S, Lin C, Cheng C. Positive association of male overactive bladder symptoms and androgen deprivation: A nationwide population-based cohort study. Anticancer Res, 39:305, 2019.
6. Sandner P, Stasch JP. Anti-fibrotic effects of soluble guanylate cyclase stimulators and activators: A review of the preclinical evidence. Respir Med, 122 (Suppl 1): S1, 2017.

Current Pharmacological Options for Treating BPH/BOO and LUTS
K-E Andersson

Benign prostatic hyperplasia (BPH) belongs to the most frequent diseases in ageing men. In the 4th decade of life, BPH is demonstrable in 30–40%, and its prevalence increases almost linearly to 70–80% in those older than 80 years. Benign prostatic syndrome (BPS), comprising lower urinary tract symptomatology (LUTS) alone or secondary to BPH, obstructing the urethra (BOO), is one of the most prevalent pathological conditions in the aging male and represents a major health care concern in most westernized countries. The causative agents and factors of BPH/LUTS are multifactorial and incompletely understood. Evidence for a two-factor model exists, those factors being bulk growth (hyperplasia and hypertrophy) and adrenergically-driven smooth muscle tone; the presence of a third factor, inflammation, has been proposed. In BPH, pathways involving androgens, oestrogens, insulin, inflammation, proliferative reawakening, stem cells and telomerase have been hypothesised in the pathogenesis of the disease. In vitro studies indicate that part of the increase in urethral pressure is caused by contraction of the smooth muscle in the prostate, prostatic capsule and prostatic urethra. Thus, it has been suggested that 40 per cent of the total urethral pressure in patients with benign prostatic hypertrophy is due to □-adrenoceptor mediated tone, and the remaining 53 per cent due to static pressure resulting from the hypertrophied prostatic bulk. Based on available, but limited, evidence from human studies a three-stage model can be hypothesized to characterize BOO-induced bladder remodeling: hypertrophy, compensation (increased detrusor contractility during the voiding phase, often in combination with filling phase detrusor overactivity) followed by a phase of decompensation (detrusor underactivity). Current drugs for treatment of BPH/LUTS include □-adrenoceptor antagonists, 5□-reductase inhibitors, muscarinic receptor antagonists, □3-adrenoceptor agonists, phosphodiesterase (PDE) type 5 inhibitors, and combinations. In a recent systematic review and meta-analysis, the authors evaluated whether newer drugs for treatment of BPH associated LUTS offered advantages over established treatments, primarily older □1-adrenoceptor antagonists (i.e., tamsulosin, alfuzosin, doxazosin). They found that none of the drugs or drug combinations used to treat BPH/LUTS was more effective than older □1-adrenoceptor antagonist monotherapy when evidence was sufficient to assess. According to another recent review, the potential new and alternative drug treatments include: drugs interfering with the nitric oxide (NO)/cyclic GMP pathway, elocalcitol (BXL-628: vitamin D3 agonist/analogue), agonists/antagonists of vasopressin and tachykinin receptors, selective cannabinoid (CB) receptors, NX-1207 (fexapotide trifutate, neuropeptide), and lonidamine (TH-070, hexokinase inhibitor). It remains to be shown if any of these drugs/principles will add anything to our therapeutic arsenal – there is still a need of new medical treatments.

Anthony Kanai
Activators Overcome Nitrergic Nerve Damage and sGC Inactivation to Treat BPH/BOO

Benign prostatic hyperplasia (BPH) is a feature of aging males. Up to half demonstrate bladder outlet obstruction (BOO) with associated lower urinary tract symptoms (LUTS), including bladder overactivity. Therapies to reduce obstruction, such as α1-adrenoceptor antagonists and 5α-reductase inhibitors, are not effective in all patients. The phosphodiesterase-5 inhibitor (PDE5I), tadalafil, is also approved to treat LUTS with BPH suggesting a key role in BPH pathogenesis for the nitric oxide (NO•) / soluble guanylate cyclase (sGC) / cGMP signaling pathway. However, PDE5I refractoriness can develop for several reasons including nitrergic nerve damage and decreased NO• production, and inflammation-related oxidation of the heme group on sCG, normally maintained in a reduced state by the cofactor, cytochrome-b5-reductase 3 (CYB5R3). Several sGC activators, such as cinaciguat (BAY 58-2667), have been developed to enhance sGC activity even in an oxidized state or in the absence of NO• and their effect on LUT function of aged mice was evaluated. sGC was expressed more in the outflow tract than in detrusor suggesting its importance as a site of action in cGMP signalling. Cinaciguat had only transient (1-hr) cardiovascular effects with oral gavage suggesting a positive safety profile. Aged mice (≥24 months) demonstrated a functional BPH/BOO phenotype, compared to adult animals (9 months), with low, delayed voiding responses and elevated intravesical pressures as measured by telemetric cystometry. This was consistent with outflow tract histological and molecular data that showed urethral constriction, increased prostate weight, greater collagen deposition and cellular hyperplasia. All changes in aged animals were attenuated by daily oral treatment with cinaciguat for two weeks, without effect on serum testosterone levels. The superiority of cinaciguat over a PDE5I was evidenced by it reversing an overactive cystometric profile in CYB5R3 smooth muscle knock-out mice, where the PDE5I, sildenafil, was ineffective. Thus, the aged male mouse is a suitable model for BPH induced BOO and cinaciguat is superior to a PDE5I to reduce obstruction and its consequent effects on bladder function.

Lori Birder
sGC Activators Dampen Sensitized Afferent Nerves, Reverse Fibrosis and Treat LUTS

In the aging population, lower urinary tract (LUT) dysfunction is common and often leads to storage and voiding difficulties classified into syndromes with overlapping symptoms. Despite the prevalence and consequences of these syndromes, LUT disorders continue to be undertreated simply because there are few therapeutic options. In addition, age-related changes in the extracellular matrix (ECM) may also impact the function of various cell types within the bladder wall. Despite having different etiologies, most chronic fibrotic disorders are associated with persistent production of similar factors including ROS that stimulate ECM production, which progressively destroys the organ's architecture and in turn its function. There is emerging evidence that changes in the activity of PNPase may lead to an abnormal urinary bladder purine metabolome, which in turn causes bladder and urethral inflammation, oxidative injury, and cellular damage. Therefore, inhibition of PNPase could be used to manipulate the urinary bladder purine metabolome and may prevent age-associated deterioration of the LUT and decrease the burden of LUT diseases.

cGMP-dependent Pathways and Smooth Muscle Contraction
Christopher Fry

Cyclic nucleotides, such as cAMP and cGMP, are essential signalling molecules that mediate a plethora of functions in different cells types. This talk will consider three aspects of cGMP activity in relation to lower urinary tract function (LUT), namely: regulation of smooth muscle contraction; regulation of transmitter release from autonomic nerves; and signalling molecules in fibrosis pathways. cGMP is generated by guanylate cyclase activity, a particulate form (pGC) that is integral to the cell membrane and a cytoplasmic (soluble) form (sGC) and each generates cGMP from GTP. Ligands for pGC include natriuretic peptides and will not be considered here and sGC is the sole target for nitric oxide (NO). A feature of sGC is a subunit that contains a heme moiety that contains reduced Fe^{2+} for enzymic activity. One aspect of the talk will discuss sGC activators that will confer enzymatic activity on the oxidised, inactive form. cGMP intracellular levels can be altered either by reducing breakdown by phosphodiesterase inhibitors (e.g. PDE5I such as sildenafil and tadalafil) or enhancing sGC activity. Part of the talk will consider the lower urinary tract/prostate distribution of NO generating enzymes, PDE subtypes and targets for cGMP such as protein kinase-G.

The contractile state of smooth muscles is a myosin-regulated system and is determined by the degree of myosin light chain phosphorylation, in turn dependent on the activity of MLC kinases or phosphorylases. cGMP importantly relaxes smooth muscle and its role in regulating kinase and in particular phosphorylase activity will be discussed through its ability to influence several intermediate components.
Another action of cyclic nucleotides is an ability to regulate transmitter release and in the context of the lower urinary tract this has been most extensively investigated in post-ganglionic parasympathetic nerves. The differential regulation of purinergic and cholinergic co-transmission offers a potential route to selectively manipulate transmitter release in the human bladder that are associated with overactive pathologies, whilst leaving physiological transmitter release more intact.
Finally, the role of cGMP in the regulation of intracellular pathways associated with deposition of extracellular matrix (EC) will be discussed. Excess EC deposition as fibrosis is a feature of many LUT pathologies that influences not only the contractile properties of smooth muscle tissues but all their biomechanical profile that affects say bladder wall compliance.
Characterisation of the role of cGMP in these pathways offers further targeted drug targets to ameliorate fibrosis dependent alteration of active and passive contractile properties of LUT musculature.
The uses of PDE5Is and sGC activators will illustrate these different facets of cGMP activity in the LUT.