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


Other Supporting Documents, Teaching Tools, Patient Education etc.

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. As ATP can stimulate P2Xs/s 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.


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 (Fe2+) as NO• does not bind to oxidized heme (Fe3+), 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 includePKG-mediated inhibition of N-type Ca2+ channels and removal of neurokinin-2 (NK2) 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 β3-
Adrenergic receptor stimulation (β₂ 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 controls⁵, 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.

Clinical relevance of PDE5 inhibitors and novel soluble guanylate cyclase activators

Marcus Drake: Professor of Physiological Urology
University of Bristol, UK

Summary

- PDE5 inhibitors and LUTS
- Limitations of PDE5 therapy
- Storage LUTS and denervation
- Soluble guanylate cyclase activator
- Early clinical use for other indications

Efficacy of PDE5 inhibitors

Men > 45 years with comorbid LUTS and ED; tadalafil improved both conditions.
IPSS improvement is largely attributed to direct (92.5%, p < 0.001) effects • rather than indirect (7.5%, p = 0.32) effects on sexual function.
Combinations using PDE5i

PDE5i + α-blocker improves IPSS (-1.8), IIEF (+3.6), Qmax (+1.5 mL/s) vs α-blockers alone (meta-analysis of 5 RCTs).

Tadalafil + finasteride; early improvement in LUTS (storage & voiding) and QoL.
  • Well tolerated, improved erectile function.


Potential mechanisms of clinical drugs

Relaxation of smooth muscle;
  • Corpora cavernosa
  • Bladder outlet (voiding)

Tadalafil + finasteride; early improvement in LUTS (storage & voiding) and QoL.
  • Well tolerated, improved erectile function.

Potential mechanisms of clinical drugs

Selectively inhibit ATP release in vitro at low frequency stimulation, without affecting ACh

Potential mechanisms of clinical drugs

In systemic application, PDE5 inhibitors influence LUT reflexes (compliance and threshold pressure) at concentrations as low as 10 picomolar.

Vehicle or
Sildenafil 10pM
Vehicle or
Sildenafil 30pM

In systemic application, PDE5 inhibitors influence LUT reflexes (compliance and threshold pressure) at concentrations as low as 10 picomolar.

PDE5i limitations in clinical use

1. Contraindications; nitrates, nicorandil, or doxazosin/terazosin.
   Unstable angina, recent MI/stroke, hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency.

2. Adverse events

3. Does not always work for improving LUTS!
Efferent inhibition (storage) OAB (storage)

Efferent excitation (voiding) Underactive bladder

**Impact of denervation**


**Mechanism of action**

PDE5i gives relaxatory effects in smooth muscle and reduces afferent activity

*In cavernosal tissue, improved blood dynamics helps erectile function*

*Not only urethral effects/ voiding LUTS; also bladder/ storage LUTS*

PDE5i prevents the breakdown of cyclic GMP, allowing nitric oxide (NO) to have a more persisting action.

*Implication that nitrergic innervation is needed*

Soluble guanylate cyclase activator (sGCa) increases production of cyclic GMP

*Implication that nitrergic innervation is not needed*

**In preclinical models of chronic kidney disease, sGC stimulators (BAY 41-2272, BAY 41-8543, BAY 60-4552, riociguat and vericiguat) and sGC activators (cinaciguat, ataciguat, BI 703704 and GSK2181236A) show renoprotective effects***

sGC stimulators and activators have a potent relaxation effect on bladder, ureter, urethra, prostate, and corpus cavernosum smooth muscle in nonpathological and pathological conditions**

Early clinical trials for use in treating heart failure†; identified to cause hypotension. Also evaluated; Raynaud’s§, glaucoma, pulmonary hypertension, memory impairment, systemic sclerosis.

**Conclusions**

PDE5 inhibitors influence LUTS, including both storage and voiding LUTS, mediated through several mechanisms of action

Storage LUTS may reflect denervation, which would preclude PDES therapy where nitrergic innervation is affected

Soluble guanylate cyclase activator is potentially not dependent on nitrergic innervation

Early clinical use for other indications has looked at heart failure and other conditions

@MarcusDrakeUro

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†Mónica FZ and Antunes E. Nature Reviews Urology 2018; 15: 42-54


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Introduction

- Efficacy of PDE5 inhibitors in ameliorating LUTS due to BPH has resulted in licensing tadalafil (5 mg daily) for its treatment. Effects include decreased international prostatic symptom scores (IPSS) and improved quality of life scores.
- Sildenafil inhibits PDE5 as it is a structural analog of cGMP but is ineffective if NO is not produced due to intrinsic nerve damage or if cGMP is oxidized (Fe³⁺) as NO⁺ can only bind to reduced heme (Fe²⁺).
- Cinaciguat is not an analog of PDE5 but directly activates sGC and the conversion of GTP to cGMP in the absence of NO⁺ or with an oxidized heme due to oxidative stress and inhibition of CyB5R3 which keeps heme in the reduced state.
- Thus, cinaciguat may be effective in patients who are refractory to PDE5 inhibitors.

The Rodent Prostate Lacks a Fibrous Outer Capsule so BPH is not Considered to Cause Outlet Obstruction

BPH is a histological evaluation which typically includes benign prostatic enlargement (BPE) and may include benign prostatic obstruction (BPO).

Histological Analysis of Adult, Aged, Aged-Treated Rat Prostates: Cinaciguat Reverses Cellular Hyperplasia and Collagen Deposition

Daily gavage with cinaciguat (10 mg/kg/d for 2 wks) or vehicle (250 µl 0.5% methyl cellulose). Trichrome stain for collagen (blue) and epithelial & stromal nuclei (brown).
Aging Often Contributes to DO—CMGs Demonstrating Decreased IC and Compliance Reversed by Cinaciguat in Aged Rats

Cinaciguat Relaxes Prostatic Smooth Muscle to Treat BPO

Summary – Putative Pathway for Development of BPH/BPE/BPO
Rubber Duck Attends a Pittsburgh Pirates Ball Game

Collaborators:
University of Pittsburgh, USA
Samuel Getchell, Yousuke Ikeda, Mark Kozlowski, Irina Zabbarova
Children’s: Carl Bates
Chemistry: James Burnett, Michael Kerner, Thomas Maskrey, Peter Wipf
Medicine: Lori Birder, William deGroat, Michael Epperly, Joseph Glorioso, William Goins, Subashan Perera, Sean Stocker, Adam Straub, Pradeep Tyagi, Naoki Yoshimura

University of Bristol, UK
Basu Chakrabarty, Marcus Drake, Christopher Fry, Hiroki Ito, Anthony Pickering

Funding Sources—grants to A. Kanai

Pittsburgh at Night

Rubber Duck Attends a Pittsburgh Pirates Ball Game
Effects of sGC Activator, Cinaciguat, on the Urothelium, Afferent Nerves and Detrusor Smooth Muscle in Mice and Rats

Lori Birder, Ph.D.
Professor of Medicine and Pharmacology
University of Pittsburgh School of Medicine

Affiliations to disclose:
None

Funding for speaker to attend:
☐ Self-funded
☐ Institution (non-industry) funded
☐ Sponsored by:

Overview

- Oxidative stress and inhibition of the reductase CyB5R3 can decrease soluble guanylate cyclase (sGC) activity.
- Cinaciguat is a small molecule soluble guanylate cyclase (sGC) activator.

- Cinaciguat has minimal effects in normal or control tissues but increased activity in pathological tissue—the opposite of PDE5 inhibitors.
- There are multiple cellular sites of action for PDE5 inhibitors and Cinaciguat in the LUT that may be involved in ameliorating LUT dysfunctions.

There are a number of potential sites for sGC expression

LUT symptoms may be due in part to oxidative stress

- Brain
  - CNS alterations lead to urgency and dysregulation of neural bladder control
- Ischemia
  - Leakage of vessels including BBB
- Detrusor/urethral muscle
  - Loss of muscle tone; ultrastructural changes including muscle damage
- Urothelium (Bladder/Urethra)
  - Increased inflammatory mediators; loss of mucosal 'seal'
- Increased symptoms

Oxidative stress can cause inflammation
- Chronic inflammation may also lead to fibrosis resulting in a stiff tissue
Cicapigat dampens sensitized bladder afferent nerves and SM activity

Cicapigat activates GC (bring about the conversion of GTP to cGMP in the absence of NO activity) expression (green) is highest in excitatory filter.

This demonstrates that cicapigat can stimulate sGC in the absence of Cyb5R3.

Cicapigat decreases fibrosis and increases compliance and force generation following radiation damage or SCI.

Daily gavage with cicapigat (10 mg/kg/day) for 2 wks (initiated 9 wks post irradiation) normalizes a number of functions.

Summary

- Sildenafil inhibits PDE5 (structural analog of cGMP) but is ineffective if NO is not produced.
- Cicapigat activates GC (bring about the conversion of GTP to cGMP in the absence of NO or with an oxidized state) can decrease sGC activity.
- While both PDE5 inhibitors and cicapigat can dampen sensitized bladder afferent nerves and micromotion, cicapigat may be effective in patients who are refractory to PDE5 inhibitors.
**Affiliations to disclose**:  
Christopher Fry

**Funding for speaker to attend**:  
☐ Self-funded  
☐ Institution (non-industry) funded  
☐ Sponsored by:  

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**W37: PDE5 Inhibitors and Novel Soluble Guanylate Cyclase Activators in the Treatment of Lower Urinary Tract Symptoms — Clinical Implications and Mechanistic Concepts**  
Chris Fry  
University of Bristol, EU

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**Smooth muscle — the molecular basis of contraction and cyclic nucleotides**

Regulation of smooth muscle contractile state is importantly determined by the activity of Myosin Light Chain Phosphatase (MLCP)

Increase activity and RELAXATION follows

Decrease activity and CONTRACTION is maintained

A ‘master regulator’ of smooth muscle contraction is Rho Kinase (ROK) and a target is MLCP

ROK

Rho–G-protein coupled signalling

**Other cellular targets for cyclic nucleotides**

Hyperpolarisation–activated cyclic nucleotide gated non-selective cation (HCN) channel. cAMP is more potent as an activator, but cGMP is also effective. Four subtypes HCN1–4.

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**Nitric oxide (NO) – cGMP pathways**

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**NO/cGMP system and detrusor relaxation**

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NO/cGMP system, nerve-mediated relaxation

Rabbit detrusor: NOS activity less in bladder than in urethra

Sheep detrusor: nerve-mediated relaxation partially blocked by ODQ

No nerve-mediated relaxation of pre-contracted tissue

Mouse detrusor: nerve-mediated contraction attenuated by sildenafil


2 min 

5 mN.mm

8 Hz

8 Hz

+1 m

M ODQ

ODQ

Sheep detrusor: nerve-mediated relaxation partially blocked by ODQ

Mouse detrusor: nerve-mediated contraction attenuated by sildenafil

Chakrabarty et al. Br J Pharmacol 2019; 176: 2227-2237

Nerve-mediated contractions – multiple transmitters

Nerve-mediated contractions are accompanied by release of ATP (both blocked by TTX)

However, the frequency dependence is different.

Atropine, to block cholinergic contractions, equalizes the frequency dependence of ATP release and tension generation

Observation: Sildenafil predominantly attenuates low frequency contractions.

Hypothesis: Sildenafil reduces nerve-mediated release of ATP.


Nerve-mediated ATP release – action of sildenafil

Nerve-mediated ATP release; role of PKG

Hypothesis: Sildenafil reduces nerve-mediated release of ATP.

Frequency dependence of sildenafil action

Sildenafil reduces nerve-mediated release of ATP.

Nerve-mediated relaxation; role of PKG

Nerve-mediated ATP release; role of PKG

ATP-transmitter release; membrane permeable cGMP derivative (8-Br-cGMP)
ATP-transmitter release; soluble guanylate cyclase activator (BAY 58-2667)

**Observation:**
A PDE-5 inhibitor reduces nerve-mediated ATP release from excitatory nerves to the bladder.

**Translational value:**
With human detrusor nerve-mediated ATP release is associated with pathological conditions such as DO.

The action of sildenafil may be through raised cGMP (8-Br-cGMP)
The action of cGMP is by PKG activation (PKG inhibitor)
sGC activators may also raise nerve terminal cGMP (BAY 58-2667)
No evidence for endogenous sGC activation (ODQ)
Less evidence for an intrinsic NOS/NO pathway (SNP, L-NAME)

Stress-activated ATP release from mucosa/urothelial cells

**Mucosa strip**

1 kPa ≈ 10 cmH₂O

**Young et al  BJU Int 2012; 110: E397 - 401**

**McLatchie et al  Br J Pharmacol 2014; 171: 3394 - 3403**
Stress-activated ATP release from urothelial cells – role of cGMP pathway

Chakrabarty et al. Br J Pharmacol 2019; 176: 2227-

Interventions to increase cGMP
- Interventions to decrease cGMP

Cyclic nucleotides act at multiple sites in bladder wall tissues – what are the functionally significant sites?

- cGMP releases pre-contracted detrusor – a key pathway is the NO : soluble guanylate cyclase : cGMP : PKG
- Presence of 'nitrergic' nerve-mediated relaxations in detrusor is equivocal
  - However, interventions that raise intracellular cGMP reduce nerve-mediated contractions
  - Effect is greater at low stimulation frequencies where ATP transmitter release is more important

Interventions that increase intracellular cGMP reduce nerve-mediated ATP release
- (PDE5 inhibition, soluble guanylate cyclase activators, cell permeable cGMP derivatives)

Interventions that increase intracellular cGMP reduce nerve-mediated ATP release
- There is less convincing evidence of a NO/NOS mediated pathway to activate soluble guanylate cyclase

Increasing intracellular cGMP (PDE5 inhibitor, cell permeable cGMP derivatives) also reduces stress-activated urothelial ATP release – less evidence for a role for soluble guanylate cyclase.

Raising intracellular cGMP represents a target to:
- reduce excitatory transmitter release associated with the overactive bladder
- reduce release of a sensory urothelial modulator

Acknowledgements

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  - The National Institutes of Health R01 DK098361
  - EU2020 InComb project

Much thanks also to:
- Basu Chakrabarty – leading on much of this work
- Callum Arthurs – ATP release from isolated pig bladder urothelial cells
- Carly McArdle – establishing ATP electrode facility to measure real-time ATP release
- John Young – initial work measuring stress-activated ATP release from isolated cells
- Linda McLatchie – excellent undergraduate students at Bristol who gathered tension and ATP release data for their final year project.
W37: PDE-5 Inhibitors and Novel sGC Activators in the Treatment of LUTS—Clinical Implications and Mechanistic Concepts

Friday, 6th September, 11:30-13:00—Hall G2

Please complete the in-app evaluation during the workshop before leaving.

Step 1, open app and select programme by day
Step 2, locate workshop
W37: PDE-5 Inhibitors and Novel sGC Activators in the Treatment of LUTS—Clinical Implications and Mechanistic Concepts
Step 3, scroll to find evaluation button
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Anthony Kanai, Ph.D.
Professor of Medicine and Pharmacology
University of Pittsburgh School of Medicine

sGC Activator, Cinaciguat, Treats Benign Prostatic Hyperplasia and the Accompanying LUTS in Aged Mice and Rats

Affiliations to disclose†:

None

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

The Rodent Prostate Lacks a Fibrous Outer Capsule so BPH is not Considered to Cause Outlet Obstruction

Histological Analysis of Adult, Aged, Aged-Treated Rat Prostates: Cinaciguat Decreases Cellular Hyperplasia and Collagen Deposition

Histological Analysis of Adult, Aged, Aged-Treated Rat Prostates: Collagen/Tissue Ratio and Epithelial and Stromal Hyperplasia in the Lateral Prostatic Lobes of Adult versus Aged Rats
Aging Often Contributes to DO—CMGs Demonstrating Decreased ICI and Compliance Reversed by Cinaciguat in Aged Rats

Daily gavage with cinaciguat (10 mg/kg/day/2 wks) or vehicle (250 μl; 89.5% H2O / 10% DMSO / 0.5% methyl cellulose).

Aging Often Contributes to DO—CMGs Demonstrating Decreased ICI and Compliance Reversed by Cinaciguat in Aged Rats

Bladder compliance, μl/cmH2O (baseline to threshold pressure)

A. control adult rat
B. control aged rat
C. control aged rat + cinaciguat
D. control adult rat + cinaciguat

Passive tension profile of detrusor strips

A. B. C.

Cinaciguat Relaxes Prostatic Smooth Muscle to Treat BPO

Two-weeks treatment with cinaciguat (5mg/kg/day) enhanced relaxation in aged (24 mo) mouse prostates—aging is associated with decreased responsiveness to PDE5 inhibitors, possibly due to oxidative stress leading to inhibition of CyB5R3 and heme oxidant.

Effect of acute cinaciguat and ODQ on relaxation in the prostates of adult, aged and treated mice

% of EFS contraction in Krebs

A. B. C.

Summary – Putative Pathway for Development of BPH/BPE/BPO

Putative Pathway for Development of BPH/BPE/BPO

CD68+ macrophage
IL-1, TNFα, TGFβ, ERK, SMAD3
fibroblast/myofibroblast (collagen secretion)
aging, oxidative stress, inflammation
dedifferentiation, apoptosis,
↑ collagen, ↑ TIMP, ↓ MMP, ↑ fibrosis

Collaborators:

University of Pittsburgh, USA
Kanai Lab: Samuel Getchell, Youko Ikeda, Mark Kozlowski, Irina Zabbarova
Children’s: Carl Bates
Chemistry: James Burnett, Michael Kerner,aber Maskrey, Peter Wipf
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Funding Sources—grants to A. Kanai

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R01-DK098361

Pittsburgh at Night

Pittsburgh Duck Attends a Pittsburgh Pirates Ball Game

Funding Sources—grants to A. Kanai

2018-07-13
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Lori Birder, Ph.D.
Professor of Medicine and Pharmacology
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Overview

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- Cinaciguat has minimal effects in normal or control tissues but increased activity in pathological tissue—the opposite of PDE5 inhibitors.
- There are multiple cellular sites of action for PDE5 inhibitors and Cinaciguat in the LUT that may be involved in ameliorating LUT dysfunctions.

LUT symptoms may be due in part to OXIDATIVE STRESS

Brain

- CNS alterations lead to urgency and dysregulation of neural bladder control

Ischemia

- (leakiness of vessels including BBB)

Urothelium (Bladder/Urethra)

- Increased inflammatory mediators; loss of mucosal 'seal'
- Increased symptoms

Detrusor/urethral muscle

- Loss of muscle tone; ultrastructural changes (including muscle damage)
- There are a number of potential sites for sGC expression in the bladder:
  - Urothelium—express sGC and produce NO
  - PMC/cortex (cGMP induces transmitter release)
  - Bladder / urethral SMC (relaxes in response to NO•)
  - BLadder / urethral SMC (relaxes in response to NO•)
  - Spinal sensory neurons (nociceptive processing)
  - EUS L6/S1 cord (prostate stromal myofibroblasts (therapeutic target for fibrosis)

Oxidative stress—can cause inflammation

Chronic inflammation may also lead to fibrosis—resulting in a stiff tissue

Healthy Tissue

- Focal injury
- Fibroblast
- Endothelial
- Smooth muscle cells (SSM)
- EdM

Fibrotic scar tissue

- Fibroblast
- Endothelial
- Smooth muscle cells (SSM)
- EdM

There are a number of potential sites for sGC expression
Cinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCI

Cinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCICinaciguat Acutely Dampens Sensitized Afferent Nerves in Bladders following Radiation Damage or SCI

Daily gavage with cinaciguat (10 mg/kg/day) for 2 wks (initiated 9 wks post irradiation)

Cinaciguat decreases fibrosis and increases compliance and force generation following radiation cystectomy.

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