

What is on the Horizon in Drug Therapy for OAB?

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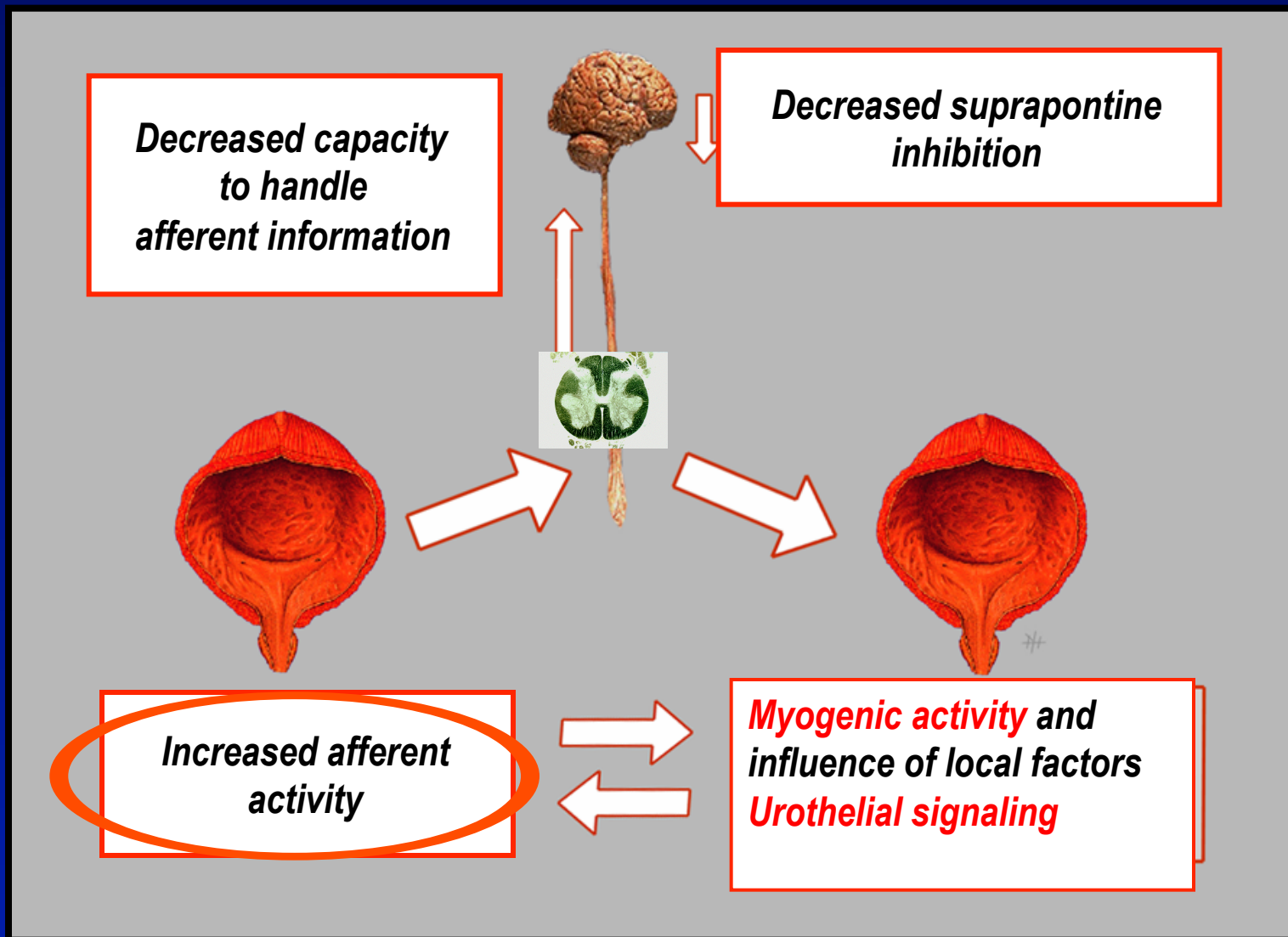


Disclosures

Consultant to:

***Allergan, Astellas, Endo, Ferrring,
Lilly, Novartis, ONO, Pfizer***

Pathophysiology of LUTS/DO/OAB



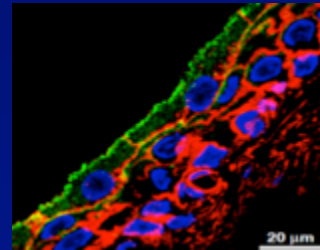
Two Defined Bladder Afferent Signaling Pathways

- *The "mucosal (urothelial)" pathway*
- *The "myogenic" pathway*

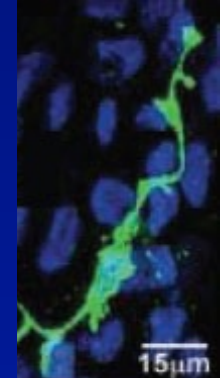
Mucosal (Urothelial) Signaling

A functional signaling unit

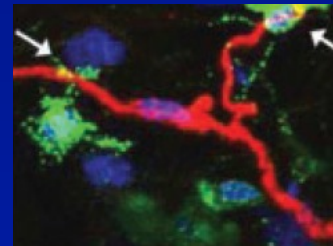
- Urothelium



- Suburothelial interstitial cells



- Afferent nerves

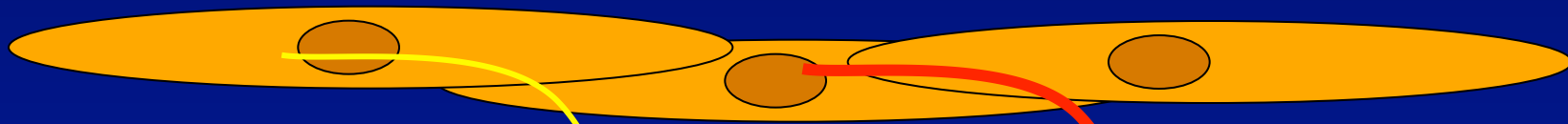
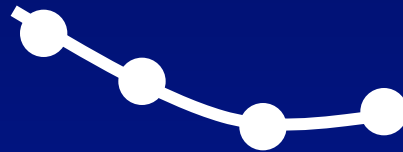


Khandelwal et al., Am J Physiol Renal Physiol (July 8, 2009).
McCloskey, Neurourol Urodyn. 2010;29(1):82-7.

Myocyte Signaling



Efferent nerve
(no activity)



Spontaneous ("myogenic")
contractions



C-fibres

Afferent activity

A δ -fibres

Afferent activity

Distension

What is on the Horizon in Drug Therapy for OAB?

- **Drugs targeting mucosal signaling**
- **Drugs targeting myocyte signaling**
- **Drugs with CNS actions**

Mucosal Signaling as a Target for Therapeutic Approaches

- *(Acetylcholine - muscarinic receptor antagonists)*
- **NGF** - NGF antibodies?
- **ATP - P2X3** - receptor antagonists?
- **K⁺ Channels** - KCNQ/Kv7 openers?
- **Prostaglandin E2** - EP1-receptor antagonists?
- **TRP - channels** - TRPV1, TRPV4, TRPA1, TRPM8
antagonists ?
- **Afferent nerves** – Botulinum toxin

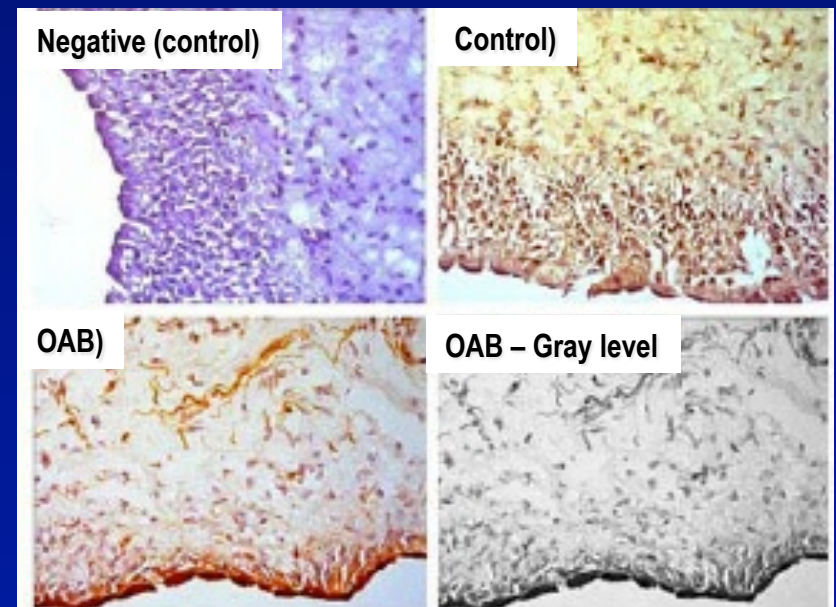
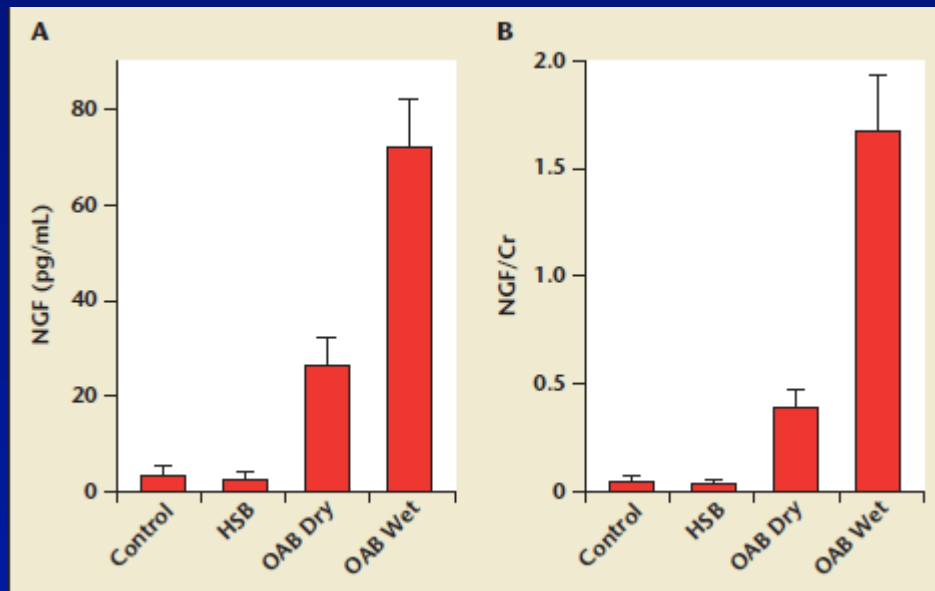
Nerve Growth Factor

Target for treatment? (tanezumab?)

Biomarker?

For diagnosis?

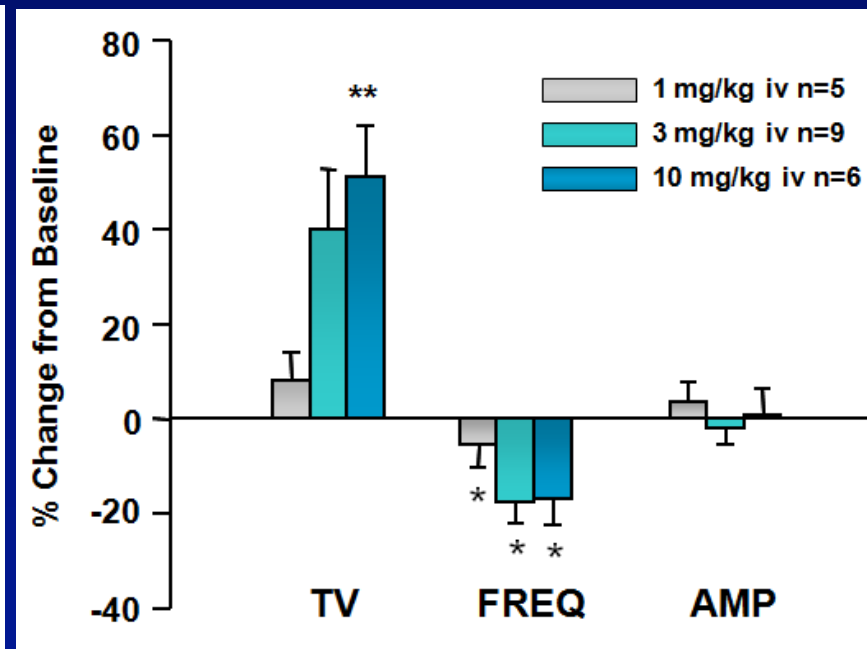
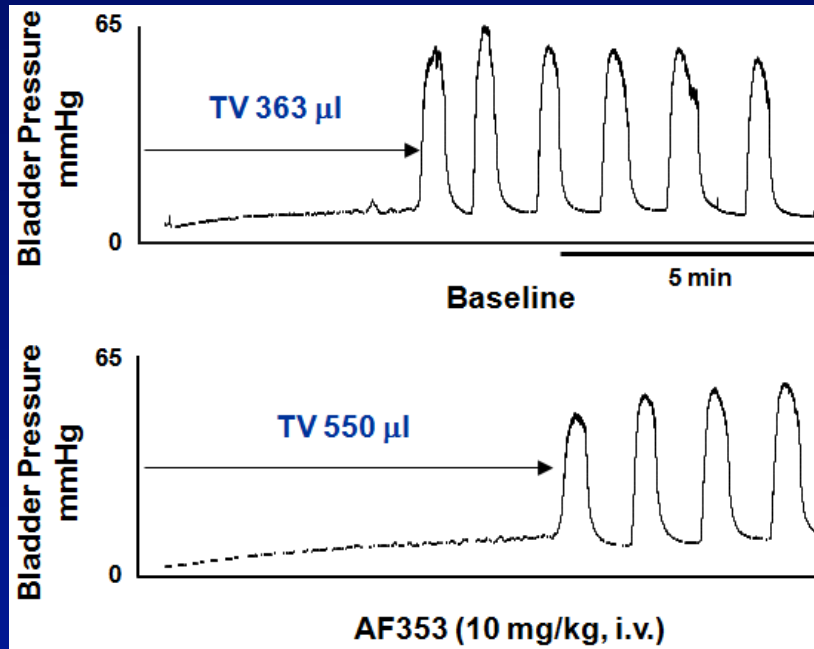
For evaluation of treatment outcome?



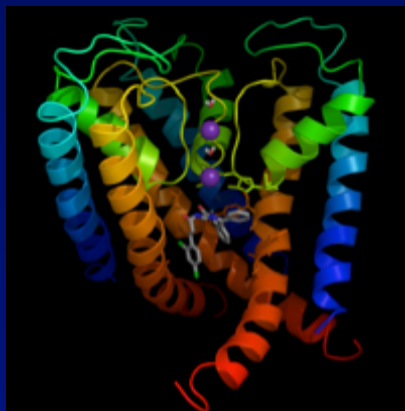
HSB = Hypersensitive Bladder Disease

Kuo et al., Rev Urol 2010;12(2/3):e69-e77
Liu et al., AUA, 2010

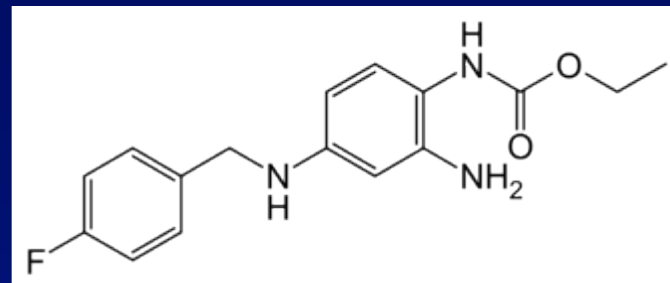
The Effect of P2X3 Antagonists on Cystometric Reflexes in Anesthetized Rats



TV = Threshold volume; FREQ = Frequency; AMP = Amplitude



Retigabine



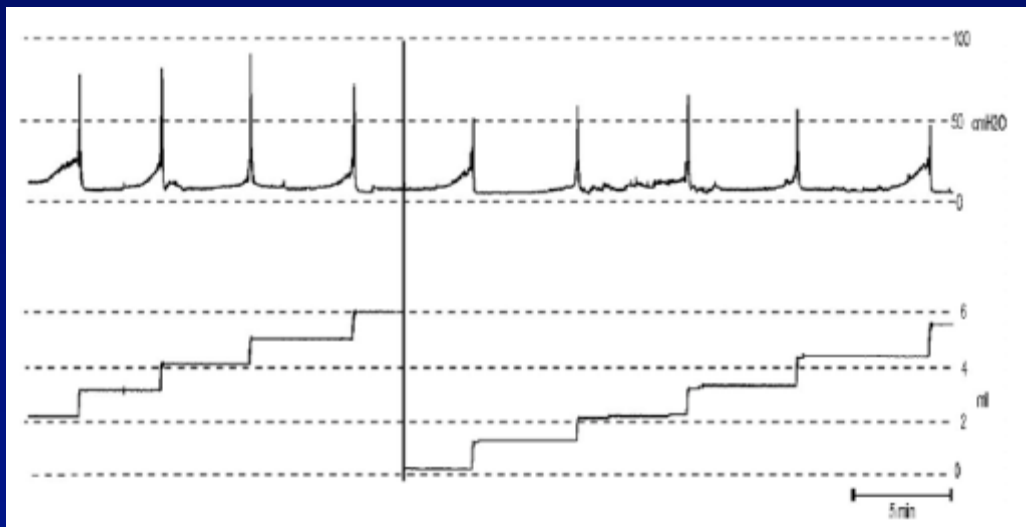
KCNQ/Kv7 - K⁺ channel opener

*Anticonvulsant, approved (FDA) for
treatment of epilepsies*

Most common adverse effects: drowsiness, dizziness,
vertigo, confusion, slurred speech

Can cause urinary retention!!

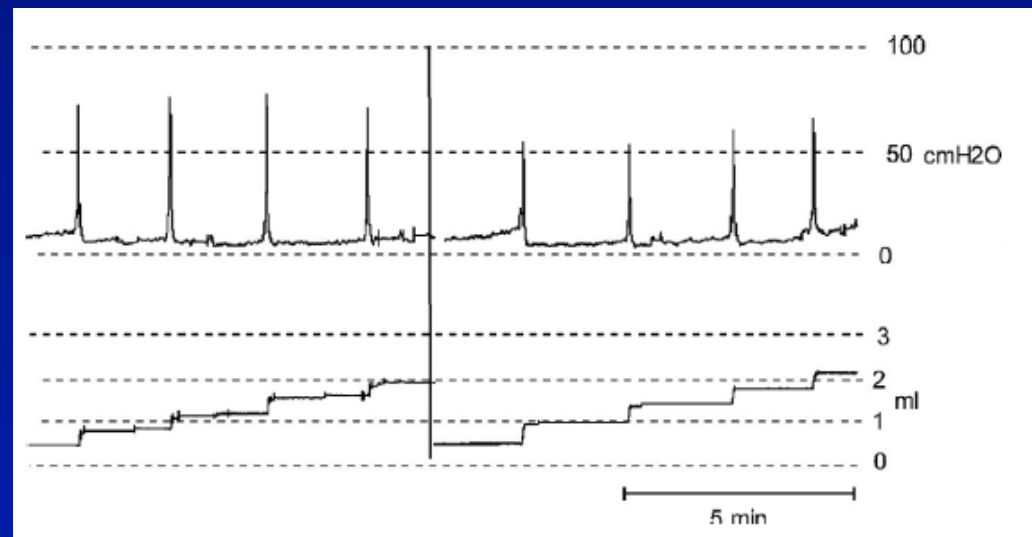
Effects of Retigabine on Rat Cystometry



Intravenous retigabine

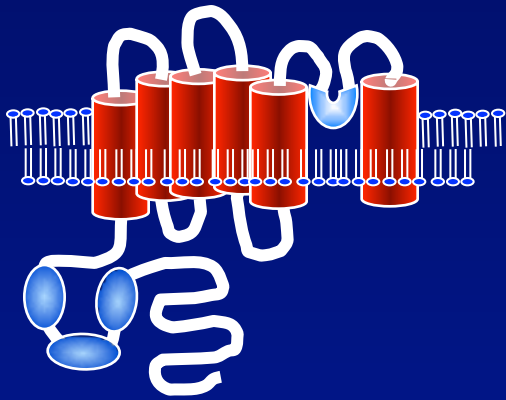


Intravesical retigabine

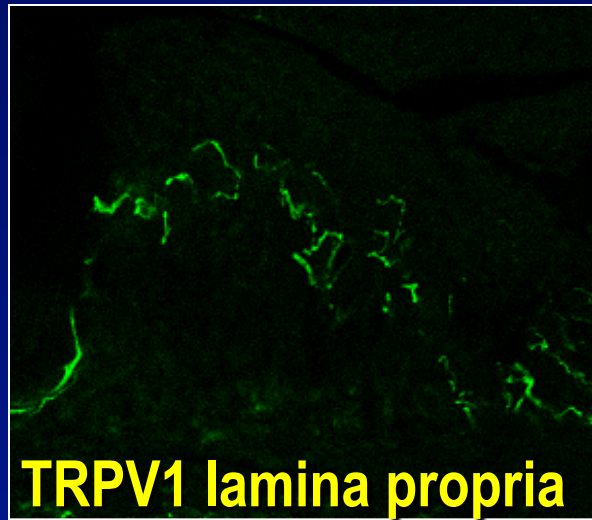


Streng et al,
J Urol. 2004 Nov;172(5 Pt 1):2054-8.

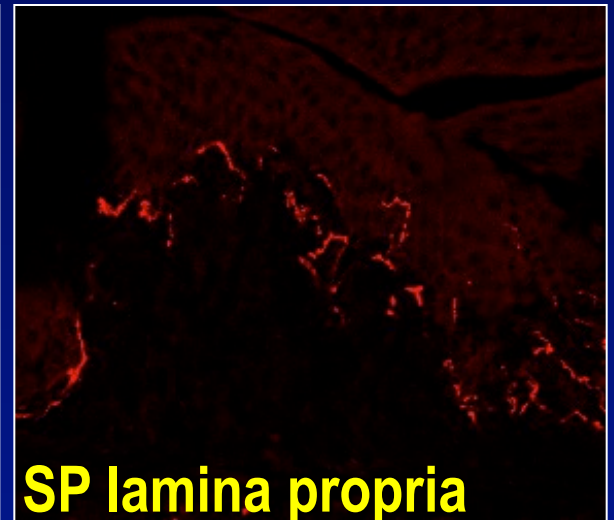
VR1 Receptors on Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) Containing Nerves in the Rat Bladder



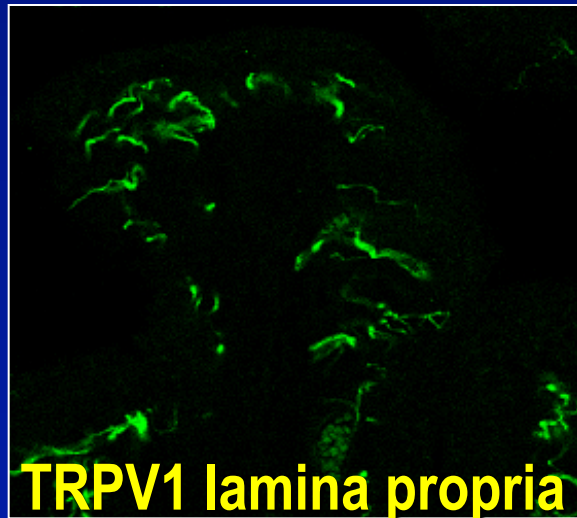
TRPV1



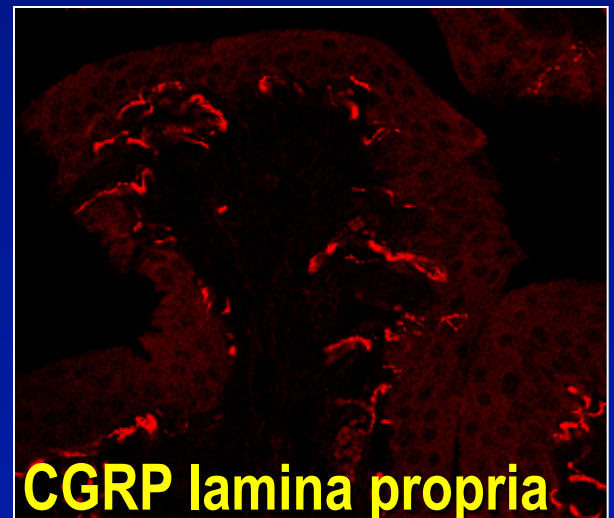
TRPV1 lamina propria



SP lamina propria



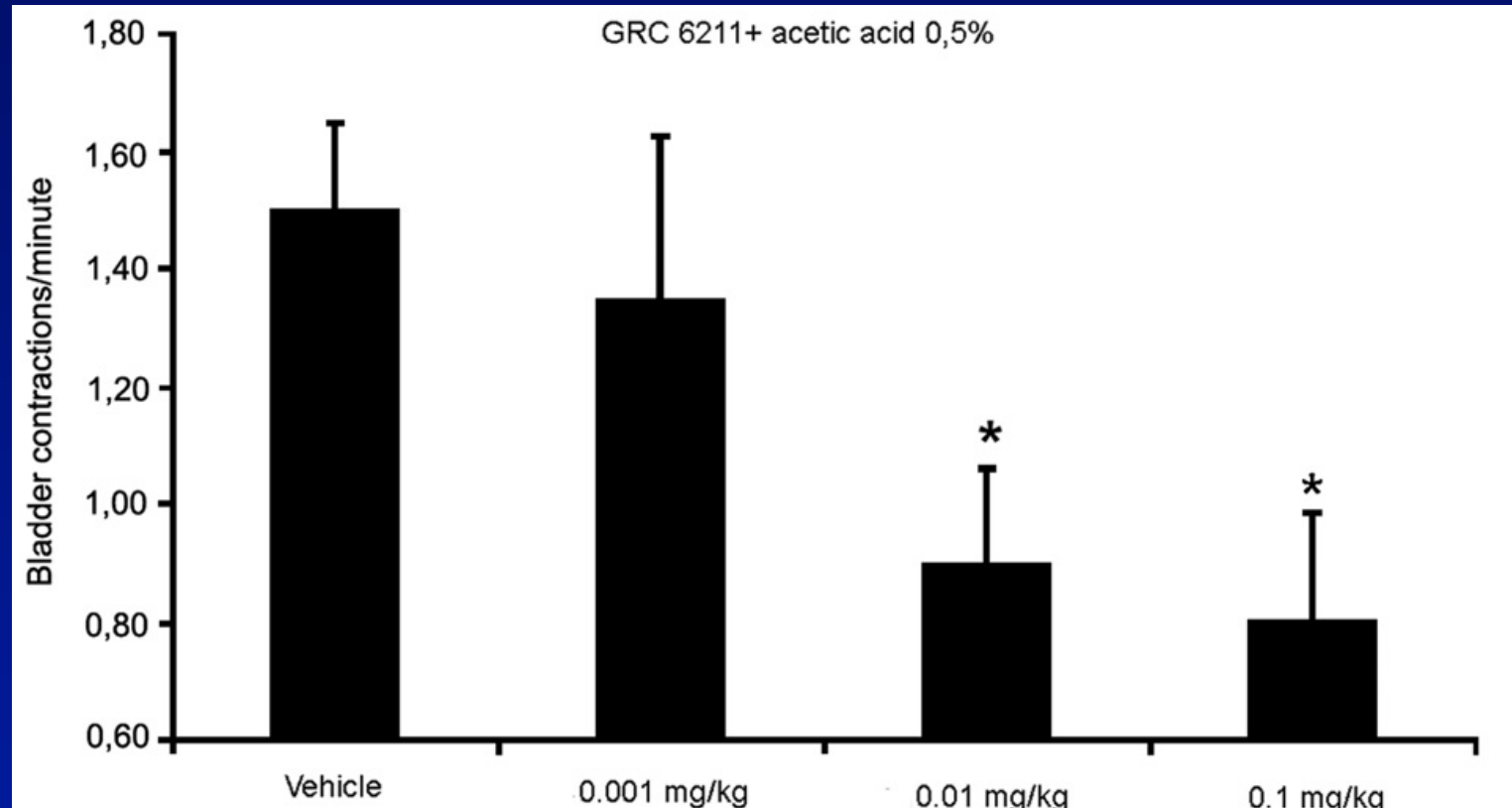
TRPV1 lamina propria



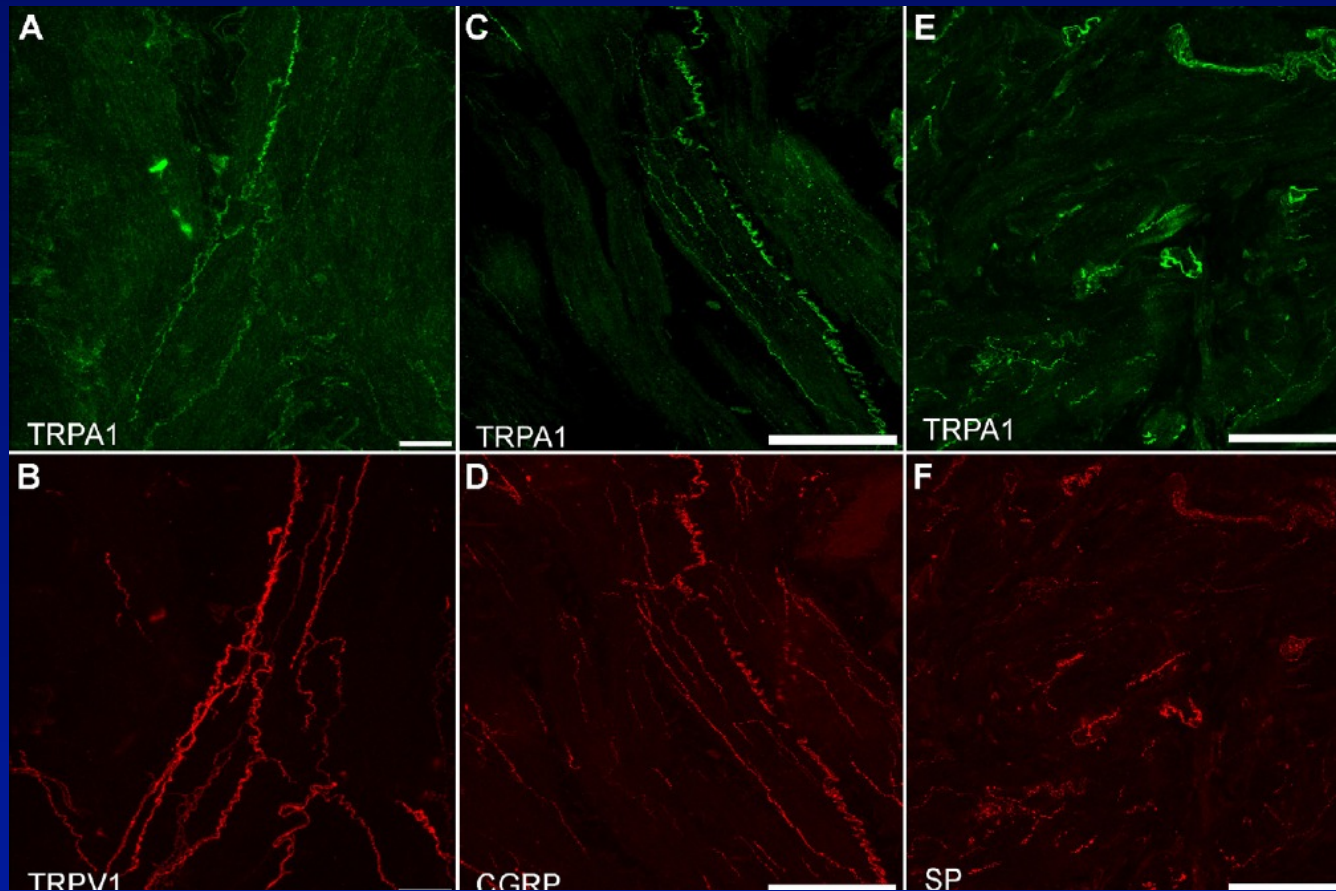
CGRP lamina propria

Avelino et al, Neuroscience
109(4):787, 2002

Effect of GRC-6211 (TRPV1 Antagonist) on Rat Bladder Activity Induced by Bladder Instillation of Acetic Acid

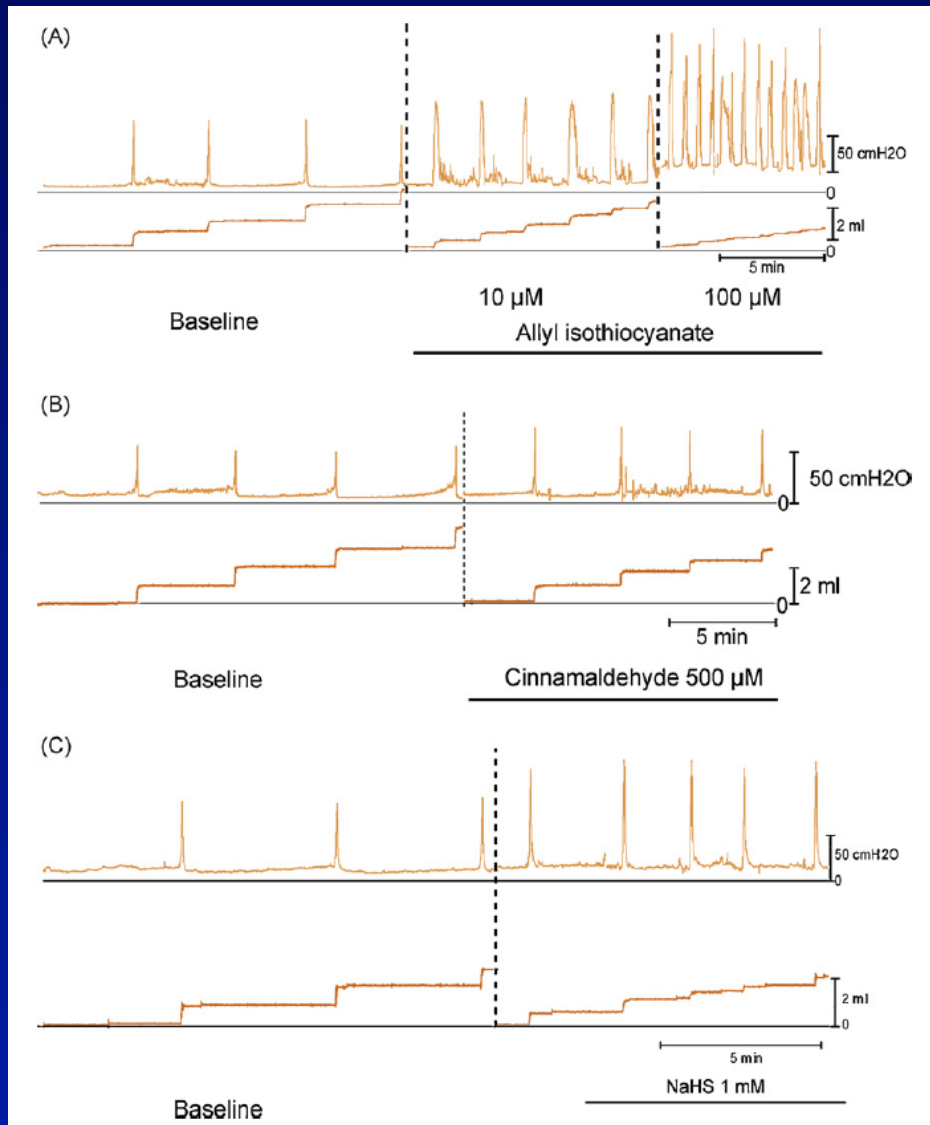


Localisation of TRPA1 in the Bladder Wall



Streng et al, 2008;53:391-399

Cystometric Effects of TRPA1 Agonists



What is on the Horizon in Drug Therapy for OAB?

- Drugs targeting mucosal signaling
- **Drugs targeting myocyte signaling**
- Drugs with CNS actions

Myocyte signaling: Therapeutic Approaches

- *(Acetylcholine - muscarinic receptor antagonists)*
- β_3 -ARs - β_3 -AR agonists
- PDE - PDE-inhibitors
- Rho-kinase - Rho kinase inhibitors?
- Cholinergic nerves – Botulinum toxin

Myocyte signaling

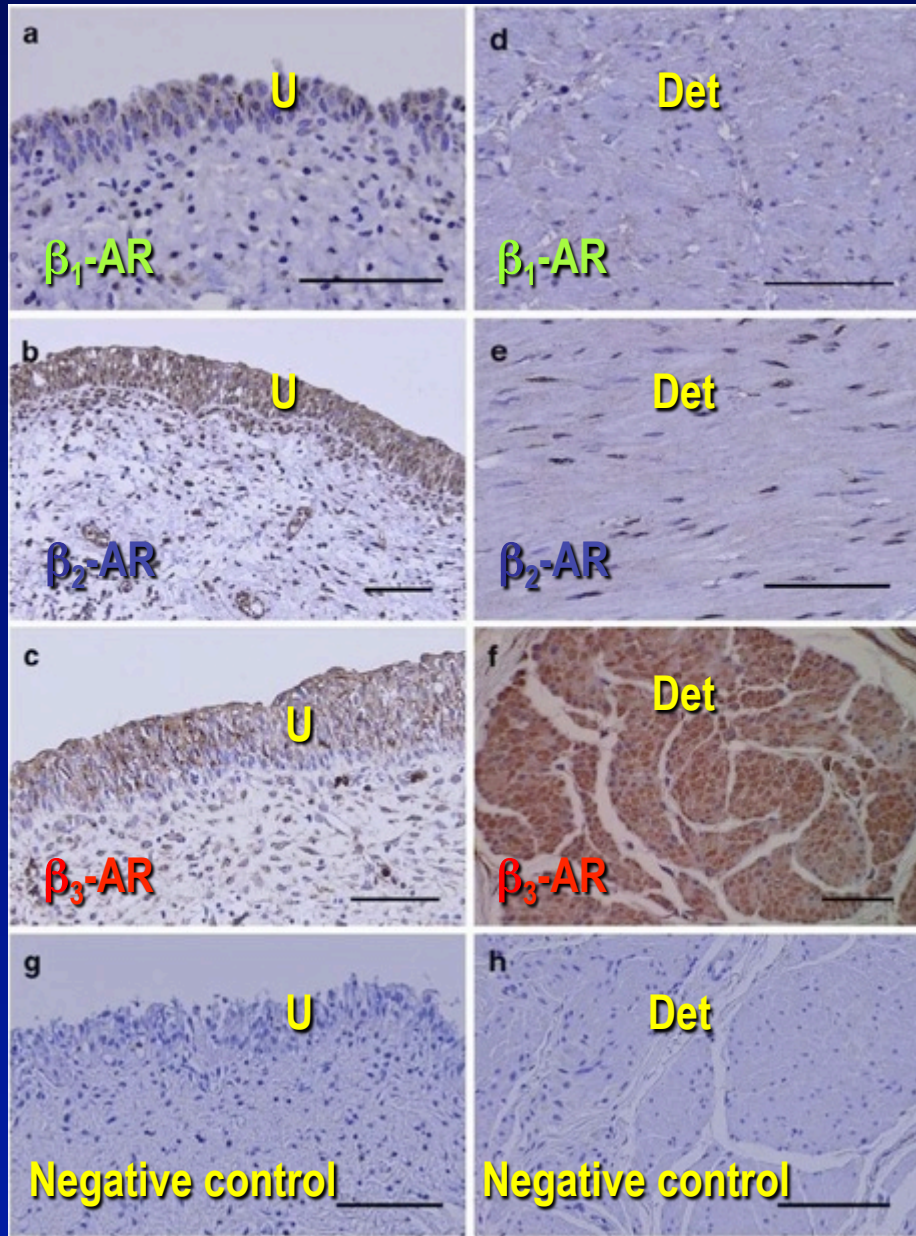
Two types of bladder contraction

Micromotions: *small units of smooth muscle contracting in an un-coordinated way during bladder filling. Stimulated of small amounts of acetylcholine from non-neuronal and/or neuronal sources. No parasympathetic outflow from the spinal cord*

Voiding contractions: *parasympathetic outflow from the spinal cord leading to co-ordinated contraction of all units of smooth muscle. Massive release of acetylcholine from the nerve terminals*

Expression and functional role of β -adrenoceptors in the human urinary bladder urothelium

Atsushi Otsuka · Hitoshi Shinbo · Rikiya Matsumoto ·
Yutaka Kurita · Seiichiro Ozono



AR = Adrenoceptor

U = Urothelium

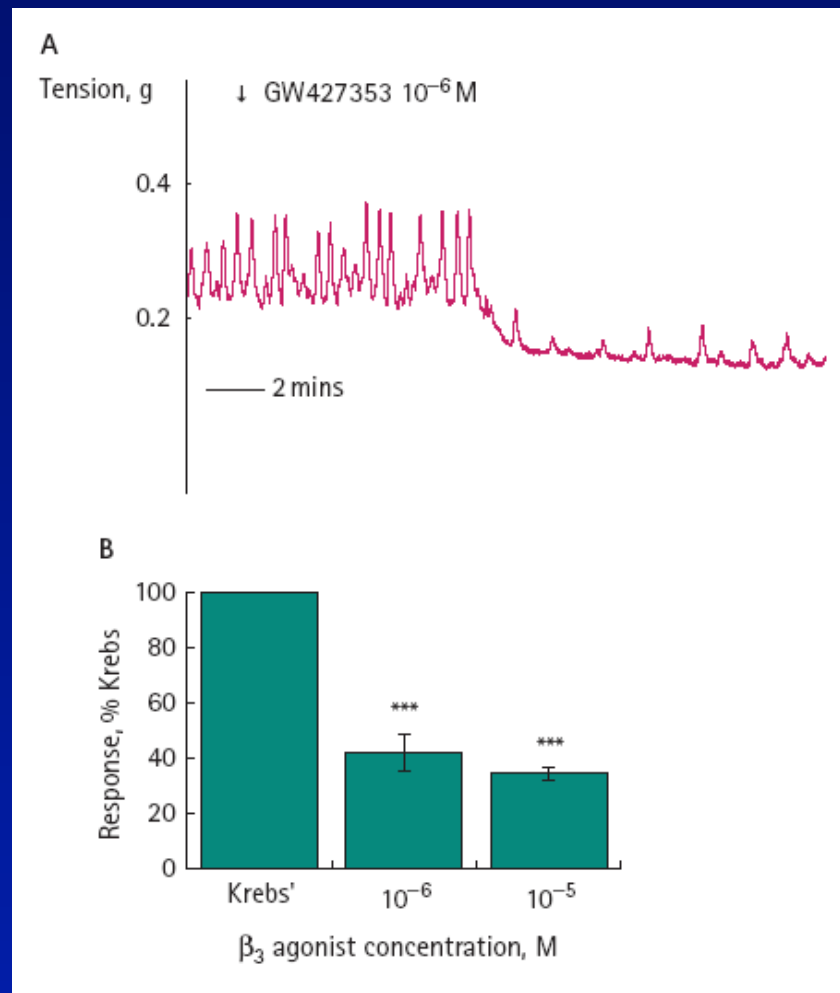
Det = Detrusor

Naunyn-Schmiedeberg's Arch Pharmacol
2008, March 1, [Epub ahead of print]

The effects of a new selective β_3 -adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder

Suzanne M. Biers*†, John M. Reynard† and Alison F. Brading*

*Department of Pharmacology, Oxford University, and †Urology, The Churchill Hospital, Oxford, UK



BJU Int. 2006 Dec;98(6):1310-4



Effects of CL316,243, a β_3 -Adrenoceptor Agonist,
and Intravesical Prostaglandin E₂ on the Primary
Bladder Afferent Activity of the Rat

Naoki Aizawa,¹ Yasuhiko Igawa,² Osamu Nishizawa,² and Jean-Jacques Wyndaele^{1*}

¹Department of Urology, Faculty of Medicine, University Antwerp, Antwerp, Belgium

²Department of Urology, Shinshu University School of Medicine, Matsumoto, Japan

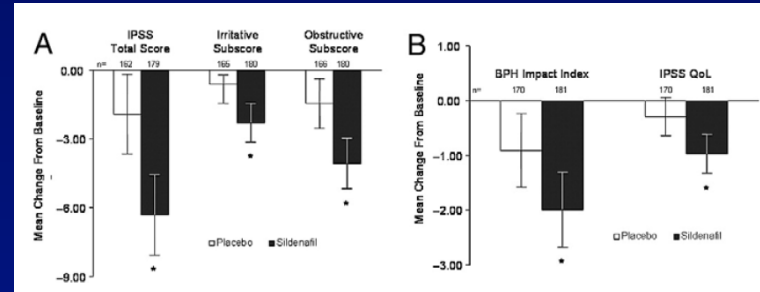
Conclusions: *The present results clearly demonstrate that the β_3 -AR agonist, CL316,243, can inhibit the mechanosensitive A δ -fibers, but not the C fibers, of the primary bladder afferents of the rat. In addition, the β_3 -AR agonist can inhibit PGE₂-induced C-fiber hyperactivity.*

Phosphodiesterase Inhibitors for Treatment of DO/OAB/LUTS

Sildenafil (PDE 5 inhibitor)

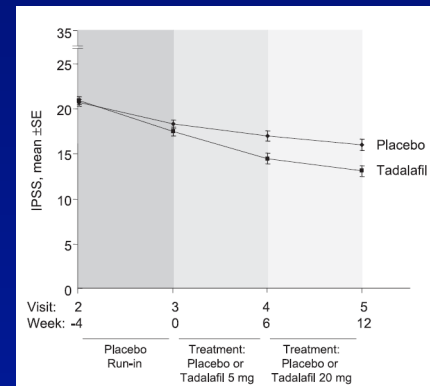
Sairam et al., BJU Int 90(9):836, 2002

McVary et al., J Urol. 2007 Mar;177(3):1071-7



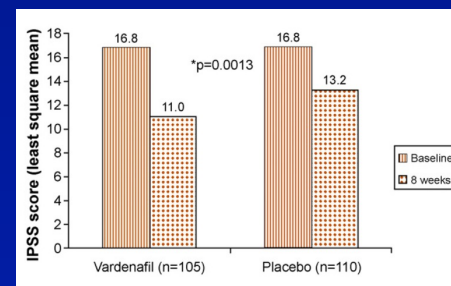
Tadalafil (PDE 5 inhibitor)

McVary et al., J Urol. 2007 Apr;177(4):1401-7



Vardenafil (PDE 5 inhibitor)

Stief et al., Eur Urol. 2008 Jun;53(6):1236-44



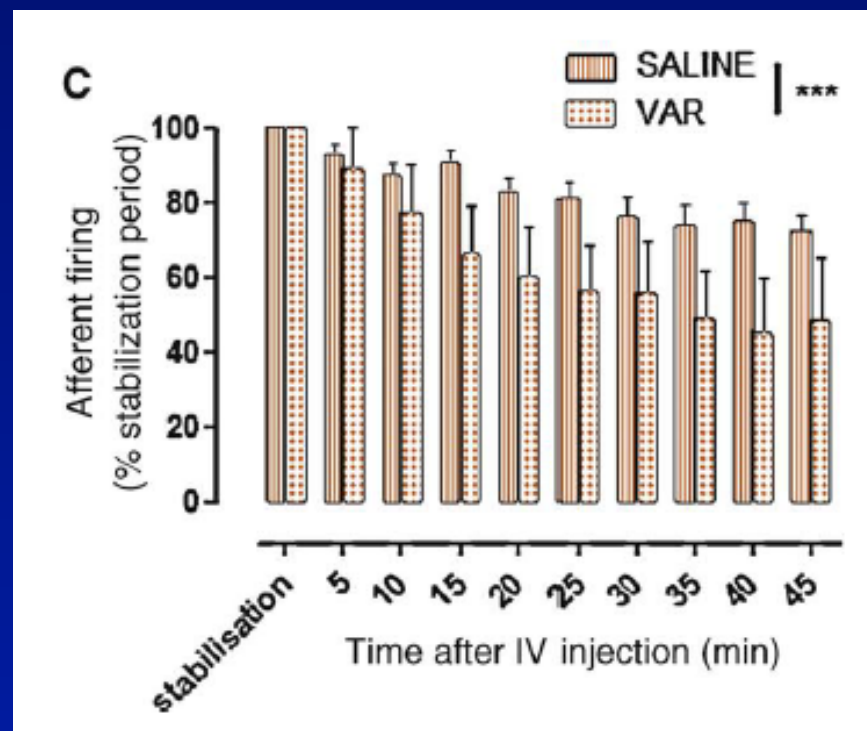
Phosphodiesterase Inhibitors for Treatment of DO/OAB/LUTS

Mechanism of action

- Modulation of afferent activity?
- Up-regulation of cGMP/PKG activity?
- Down regulation of Rho kinase activity?
- Increasing pelvic organ blood flow?
- Reduction of inflammation?

Vardenafil Decreases Bladder Afferent Nerve Activity in Unanesthetized, Decerebrate, Spinal Cord-Injured Rats

Delphine Behr-Roussel^{a,d}, Stephanie Oger^{a,d}, Stéphanie Caisey^{a,d}, Peter Sandner^b, Jacques Bernabé^{a,d}, Laurent Alexandre^a, Francois Giuliano^{c,d,*}



What is on the Horizon in Drug Therapy for OAB?

- Drugs targeting mucosal signaling
- Drugs targeting myocyte signaling
- **Drugs with CNS actions**

What is on the Horizon in Drug Therapy for OAB?

- *Opioids?*
- *5-HT/NA reuptake inhibitors?*
- *Gabapentin analogues?*
- *NK-1 receptor antagonists?*
- *GnRh antagonists?*

Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study

M. R. Safarinejad & S. Y. Hosseini

Urology Nephrology Research Centre, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

No of voids/24 h:	9.3 – 5.1 (P<0.001)
Mean voided volume:	158 – 198 ml (P<0.001)
No of incontinence episodes	3.1 – 1.6 (P<0.001)

”In patients with non-neurogenic IDO tramadol provided beneficial clinical and urodynamic results”

Pharmacological Targets in LUT Dysfunction

Treatments based on effects on:

Urothelial signaling:

Acetylcholine receptors; P2X3 receptors?; KCNQ/Kv7-channels?; TRP – channels?

Myocyte signaling:

Acetylcholine receptors; β_3 -ARs; PDEs; Rho-kinase?

Central control:

Opioid receptors?, 5-HT/NA reuptake mechanisms?, $\alpha_2\delta$ subunit of voltage-regulated Ca^{2+} channels?, NK-1 receptors?, GnRH?

What is on the Horizon in Drug Therapy for OAB?

Future approaches

Monotherapy: requires multiple drugs with different mechanisms of action, since OAB is a multifactorial disorder

Combination therapy: e.g., α 1-receptor blocker + 5 α -reductase inhibitor, α 1-receptor blocker + antimuscarinic, etc