Progress and Opportunities for Pharmacological Treatments

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  Allergan, Astellas, Bayer, Ferring
- Conflicts of interest: None

Progress and Opportunities for Pharmacological Treatments

Focus on:

Significance

State-of-the-Art-Knowledge

Knowledge Gaps

Research Opportunities

Progress and Opportunities for Pharmacological Treatments

Outline

What is available?

What do we want?

What is promising?

- advantages
- limitations

What is available?

- *Antimuscarinics block muscarinic receptors, efficacious but adverse effects, still a first line pharmacological therapy*
- *β_3–AR agonists (mirabegron) relax the bladder, efficacious, fewer adverse effects than antimuscarinics, first line alternative pharmacological therapy*
  Knowledge gap: long term data
- *Phosphodiesterase-5 inhibitors (tadalafil) improve male LUTS, mechanism unclear. Do they work in women?*
  Research opportunity
- *Onabotulinumtoxin A inhibits transmitter release from nerves (afferent and motor) and urothelium, efficacious but second line pharmacological therapy*

What Do We Want?

OAB is multifactorial

– is it possible to find a drug that improves everybody?

Knowledge gap: mechanistic studies

OAB is a filling disorder

– is there a common mechanism that can be targeted?

Knowledge gap: mechanistic studies

OAB is a “benign” disorder

– adverse effects must be few and mild

OAB – Pathophysiology

Both the overactive bladder (OAB) syndrome and detrusor overactivity (DO) are multifactorial disorders

Are multiple, separate pathways involved, each contributing to the disorder ?
Knowledge gap: mechanistic studies

Do all pathophysiologies have a common pathway?
Knowledge gap: mechanistic studies

OAB – Suggested Underlying Mechanisms

Uroepithelial factor:

Sensor moleculars: ACh, ATP, NGF, TRPV1

Myogenic factor:

Detrusor spontaneous contraction
Hypersensitivity to incoming signals

Neurogenic factor:

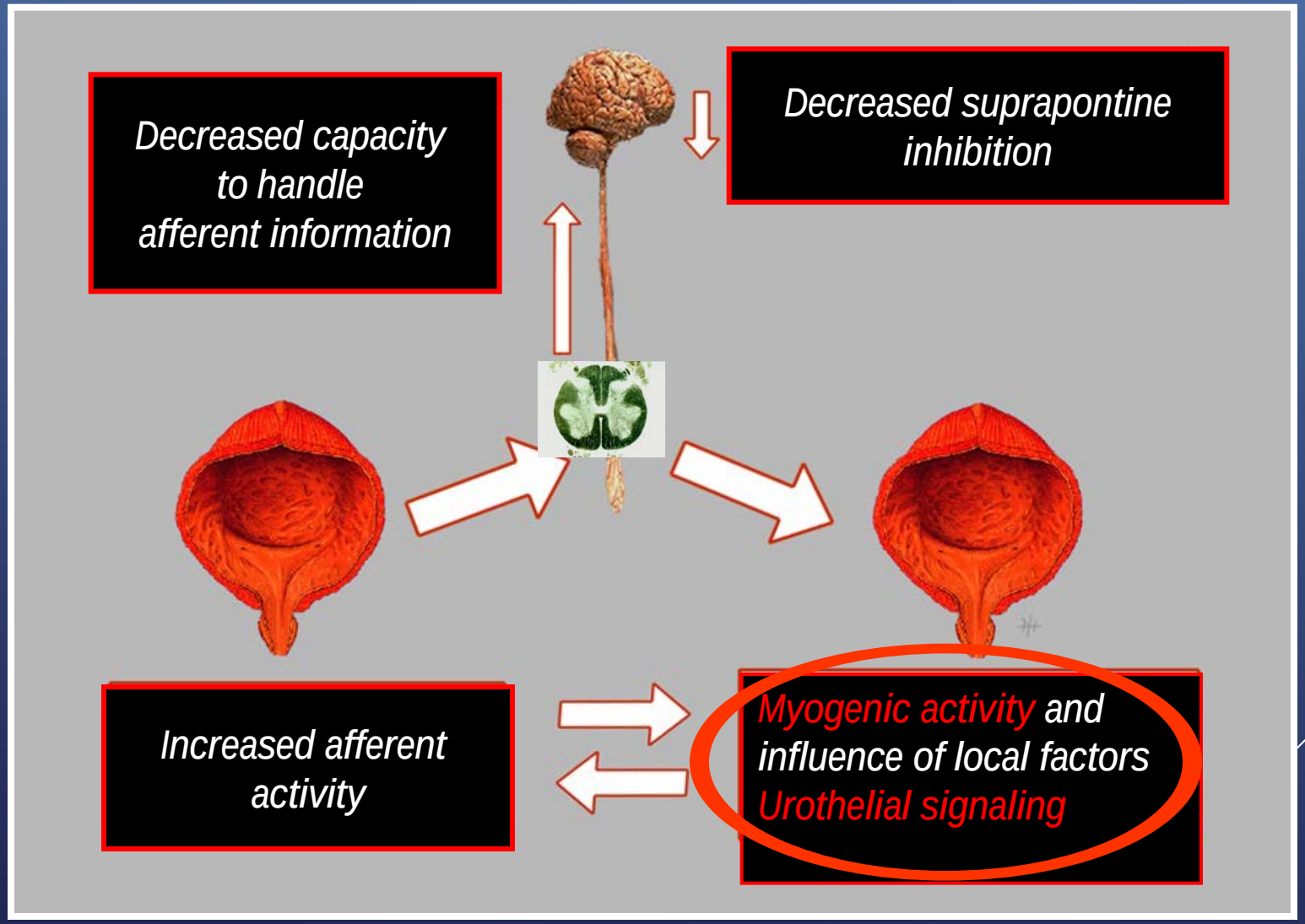
Abnormal afferent excitability
Abnormal sensory process

Specific factor:

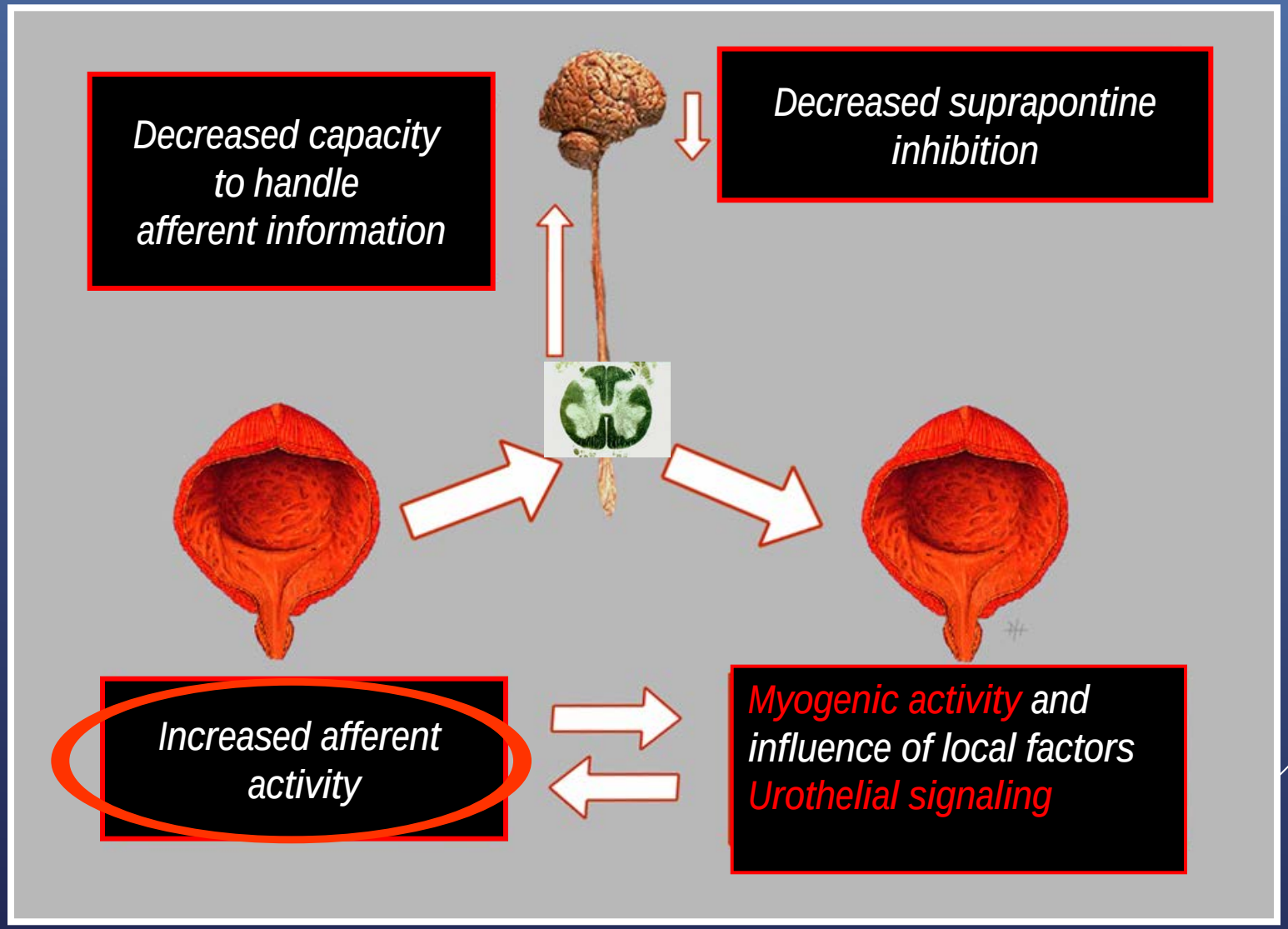
Bladder outflow obstruction
Metabolic syndrome and diabetes mellitus
Inflammation

Meng et al., LUTS ;2012: 4:38-55

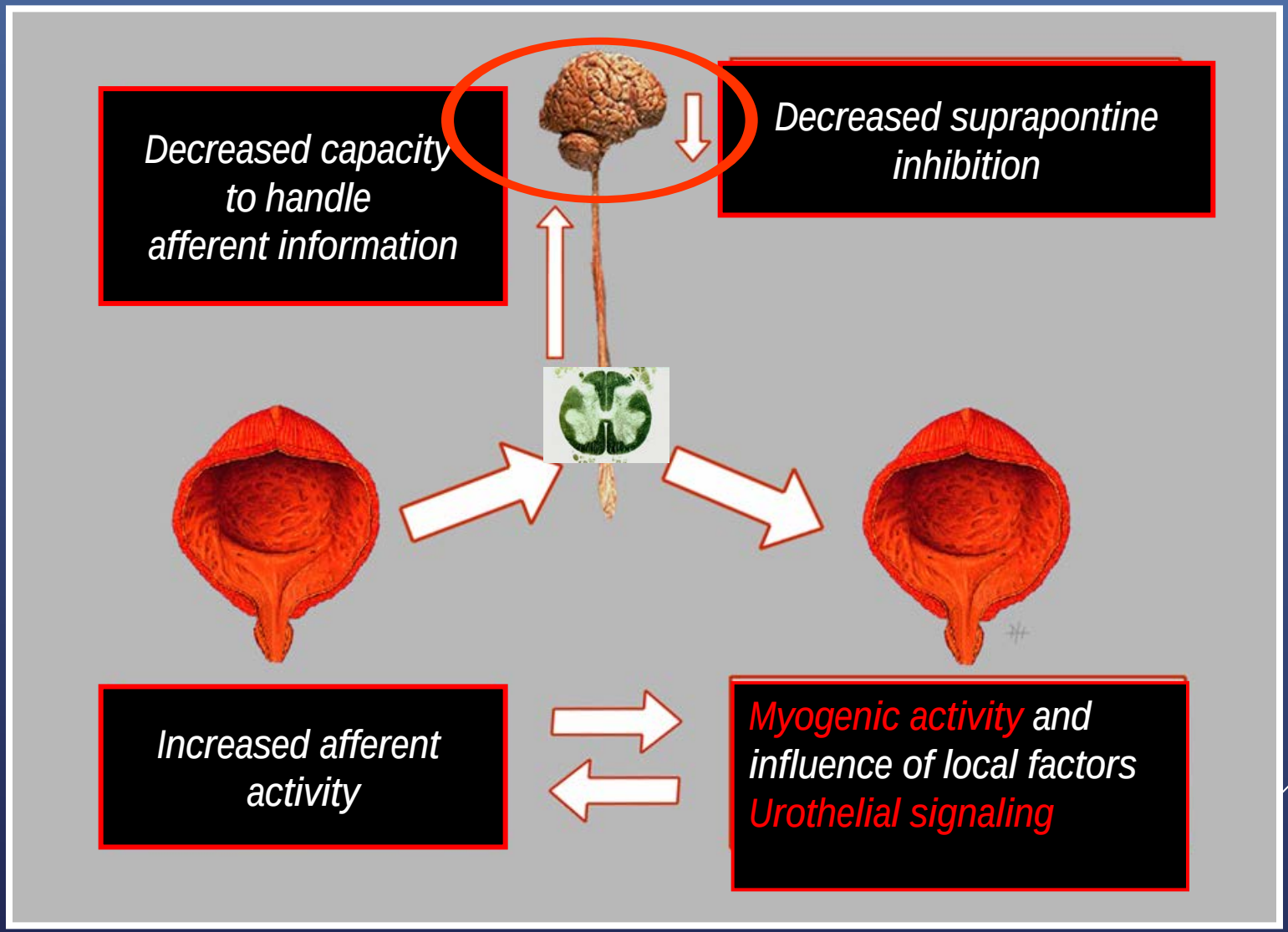
Pathophysiology of LUTS/DO/OAB



Pathophysiology of LUTS/DO/OAB



Pathophysiology of LUTS/DO/OAB



OAB – Targets for Drug Treatment

Levels of intervention

Bladder: *factors and structures in the bladder wall*

Afferent nerves: *Afferent signaling from the bladder*

CNS: *Central handling of afferent information*

Bladder: *Efferent neurotransmission*

What is Promising?

Targets and Drugs: Research Opportunities

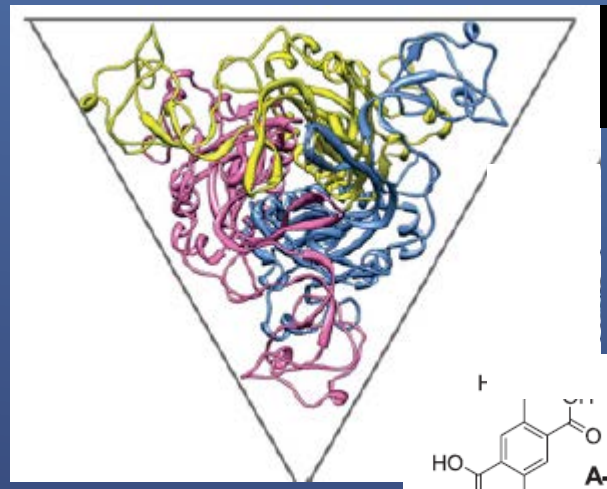
- *Purinergic receptors - Antagonists*
- *Cannabinoid system - Agonists – Antagonists - Inhibitors*
- *TRP channels - Antagonists*
- *Prostanoid Receptors – Antagonists*
- *Nerve Growth Factor - Inhibitors*
- *Rho- kinase - Inhibitors*
- *K+ channels - Openers*
- *Centrally acting drugs*

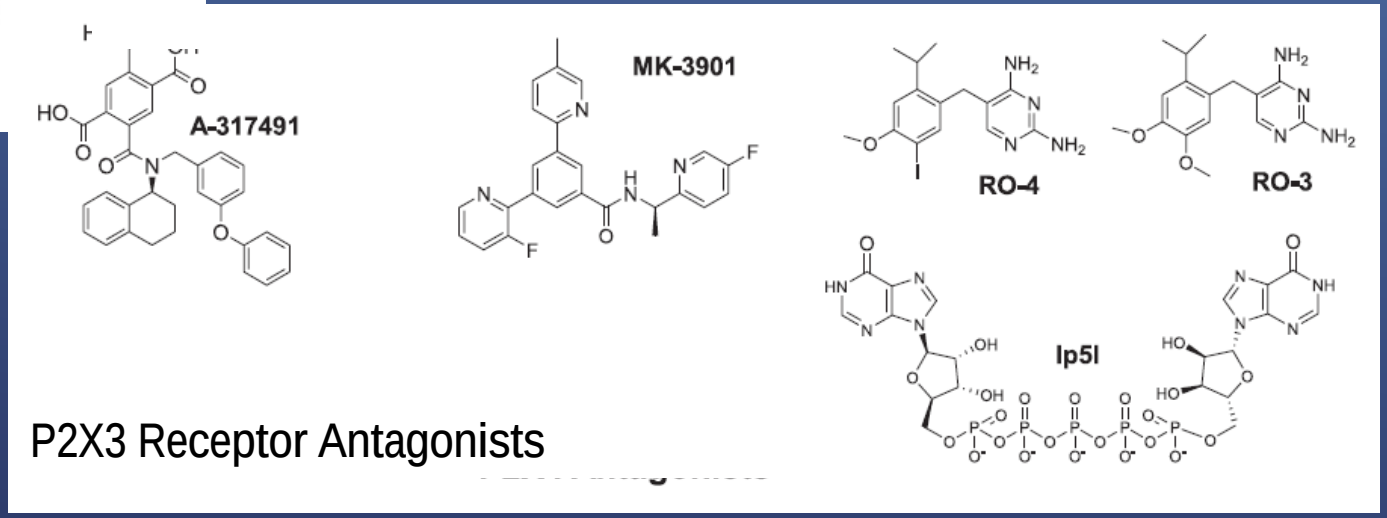
What is Promising?

Targets and Drugs: State-of-the-Art-Knowledge

- *Purinergic receptors - Antagonists*
- *Cannabinoid system - Agonists – Antagonists - Inhibitors*
- *TRP channels - Antagonists*

The P2X3 Receptor

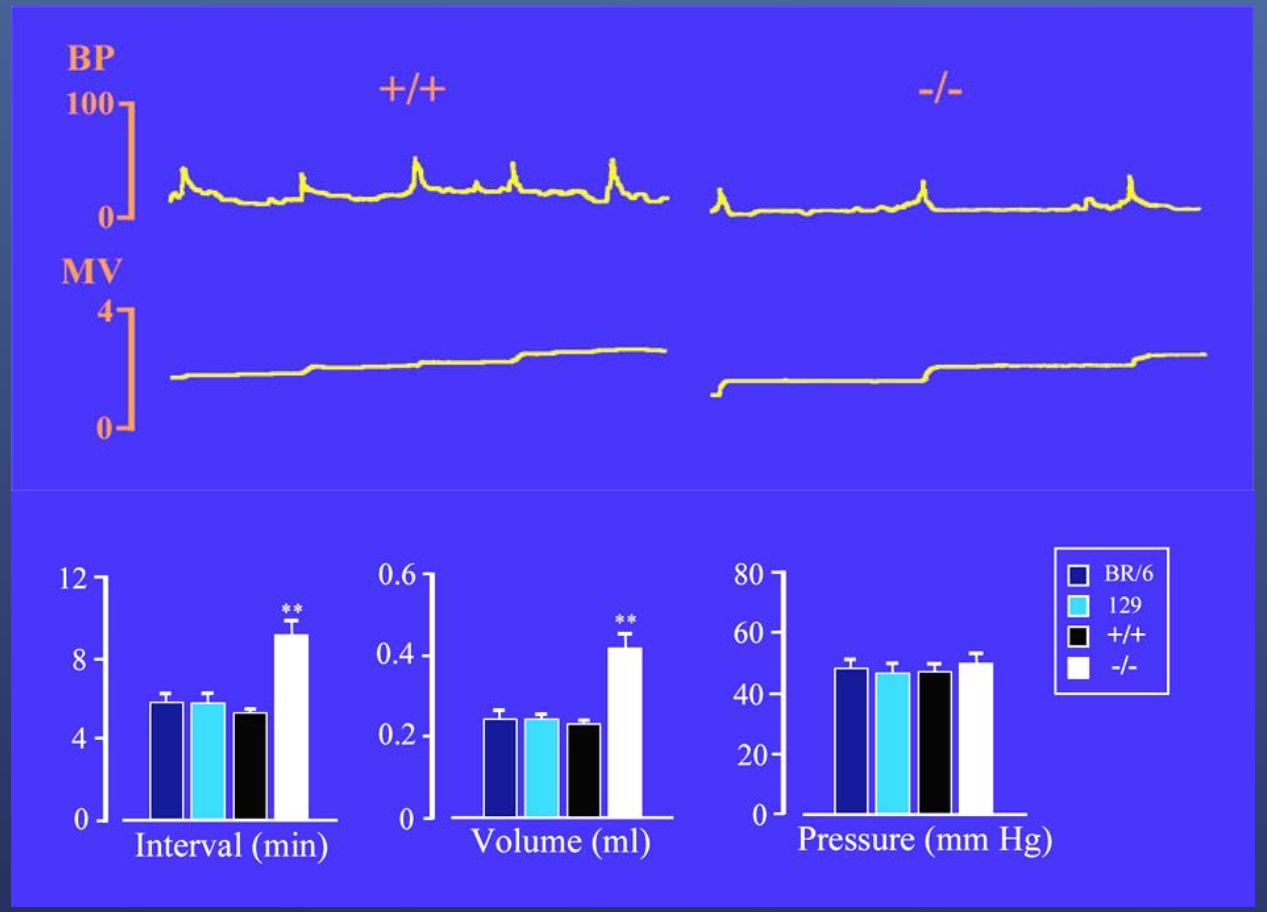




P2X3 Receptor Antagonists

North and Jarvis, Mol Pharmacol., 2013 Apr;83(4):759-69

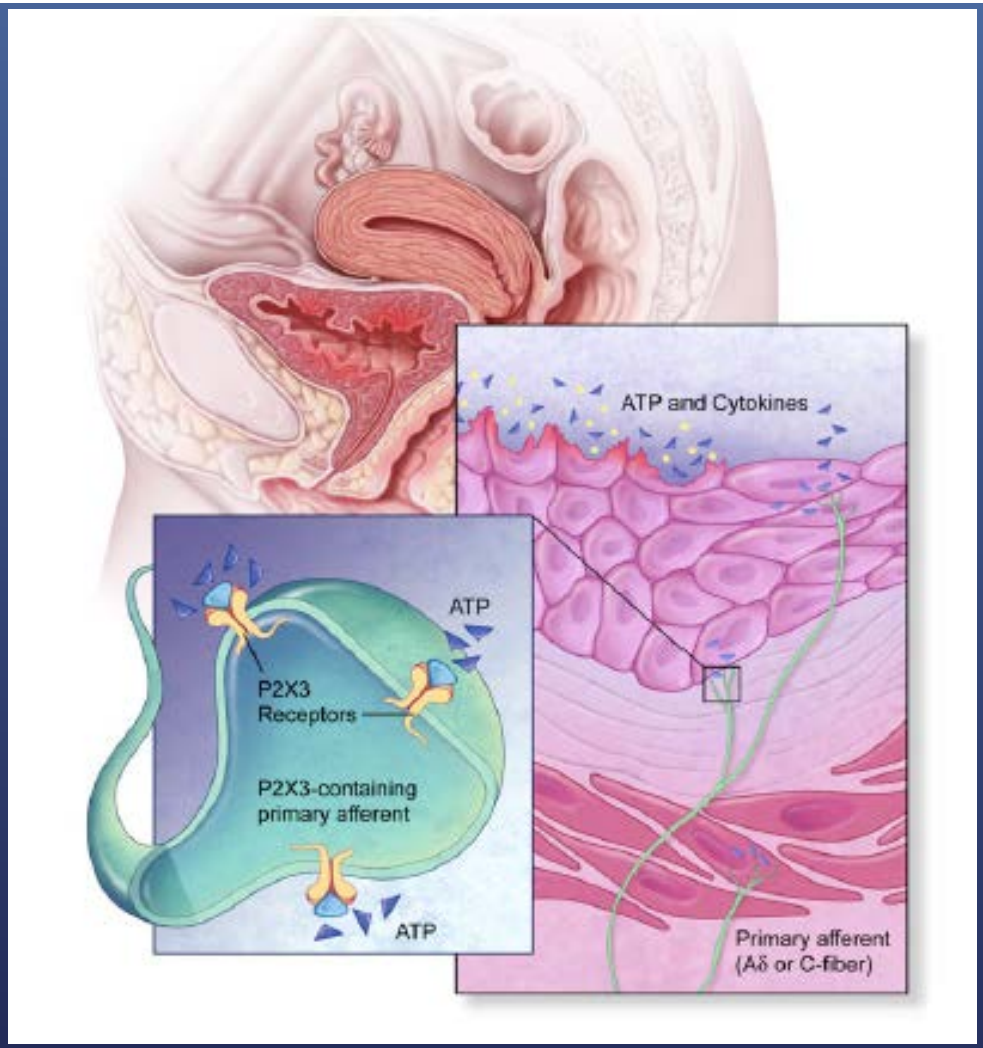
Bladder Function in P2X3-deficient Mice



Cockayne et al. Nature 407:1011, 2000

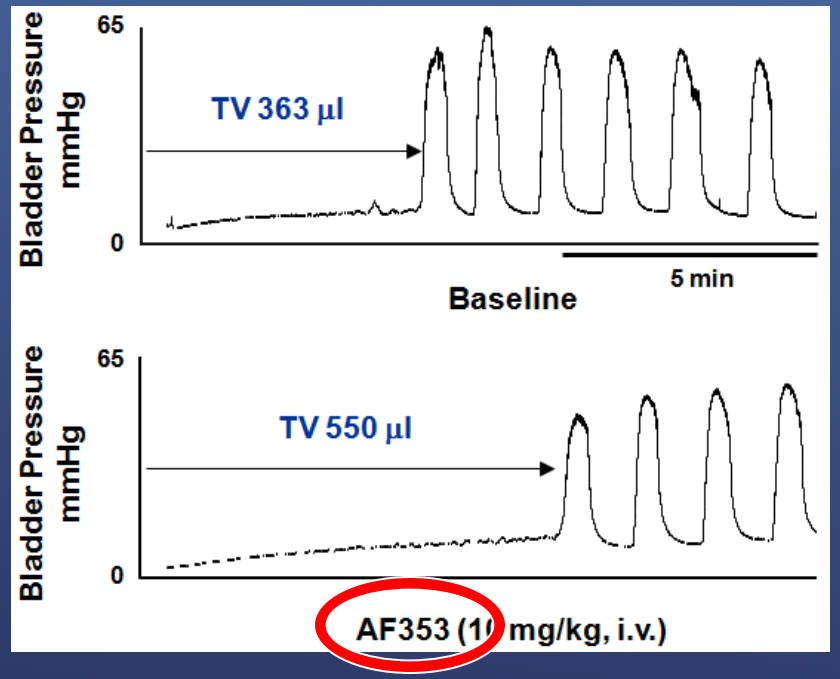
In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization

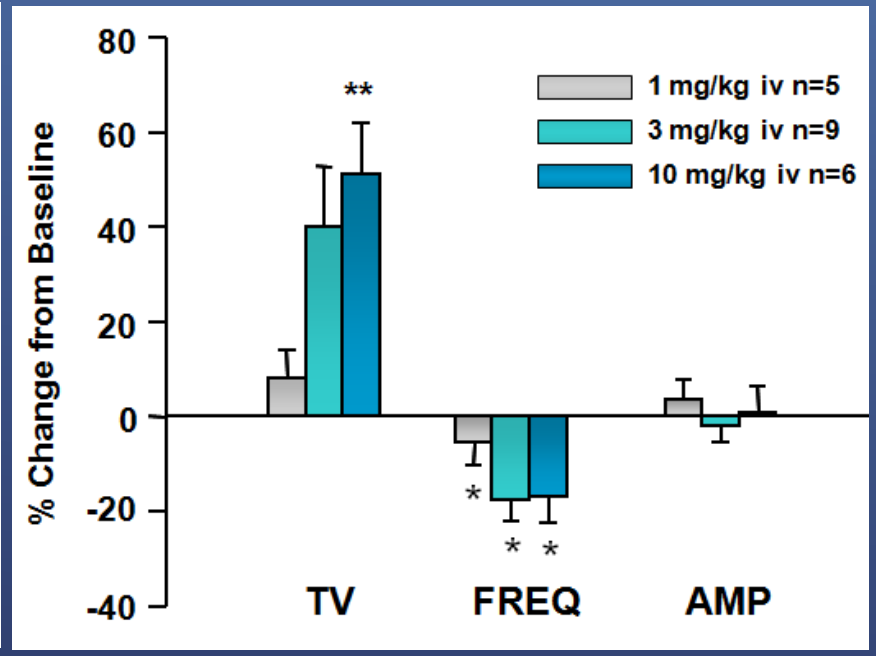
Anthony P. Ford



Purinergic Signalling (2012) 8 (Suppl 1):S3–S26

The Effect of a P2X3 Antagonist on Cystometric Reflexes in Anesthetized Rats

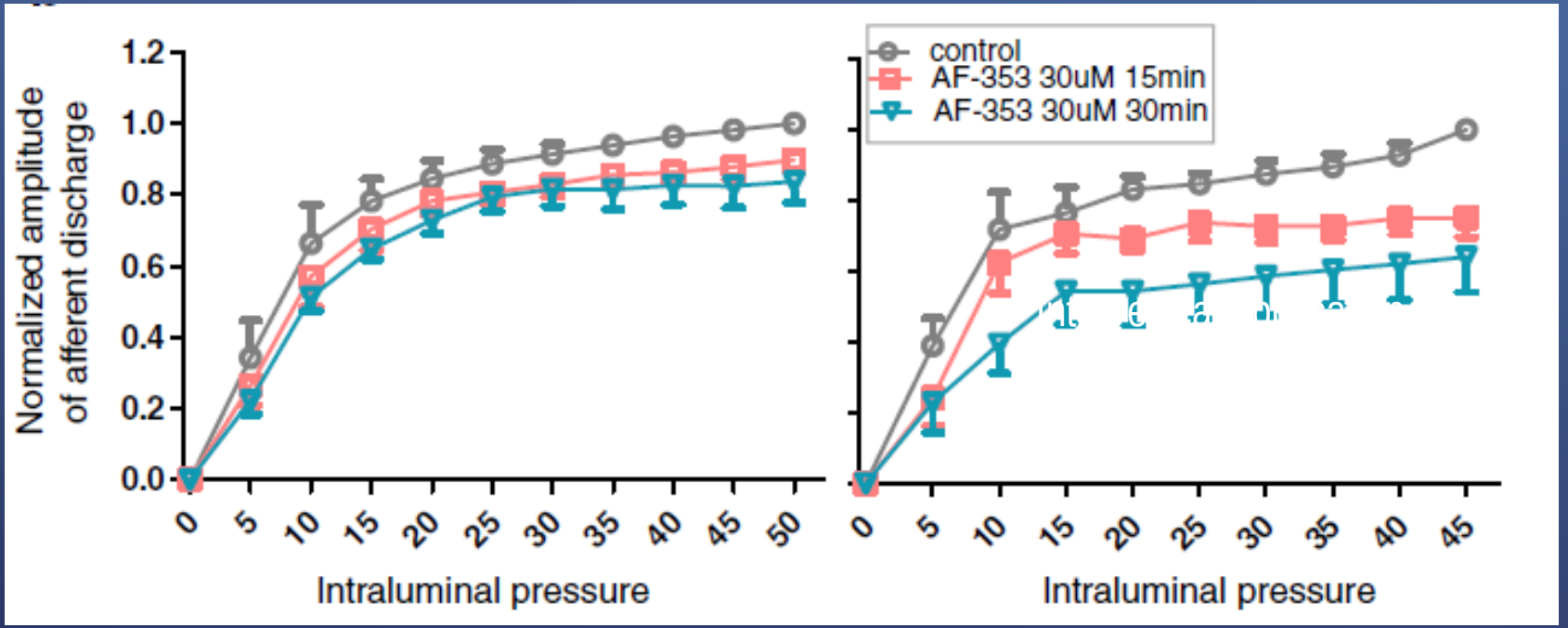




TV = Threshold volume; FREQ = Frequency; AMP = Amplitude

Ford and Cockayne,
Handb Exp Pharmacol. 2011;(202):485-526.

Effects of AF-353 on Afferent Signaling from the Bladder



Purinergic Signalling (2012) 8 (Suppl 1):S3–S26

What is Promising?

P2X3 receptor antagonists

Good preclinical rationale

New promising drug candidates

No clinical experiences published

What is Promising?

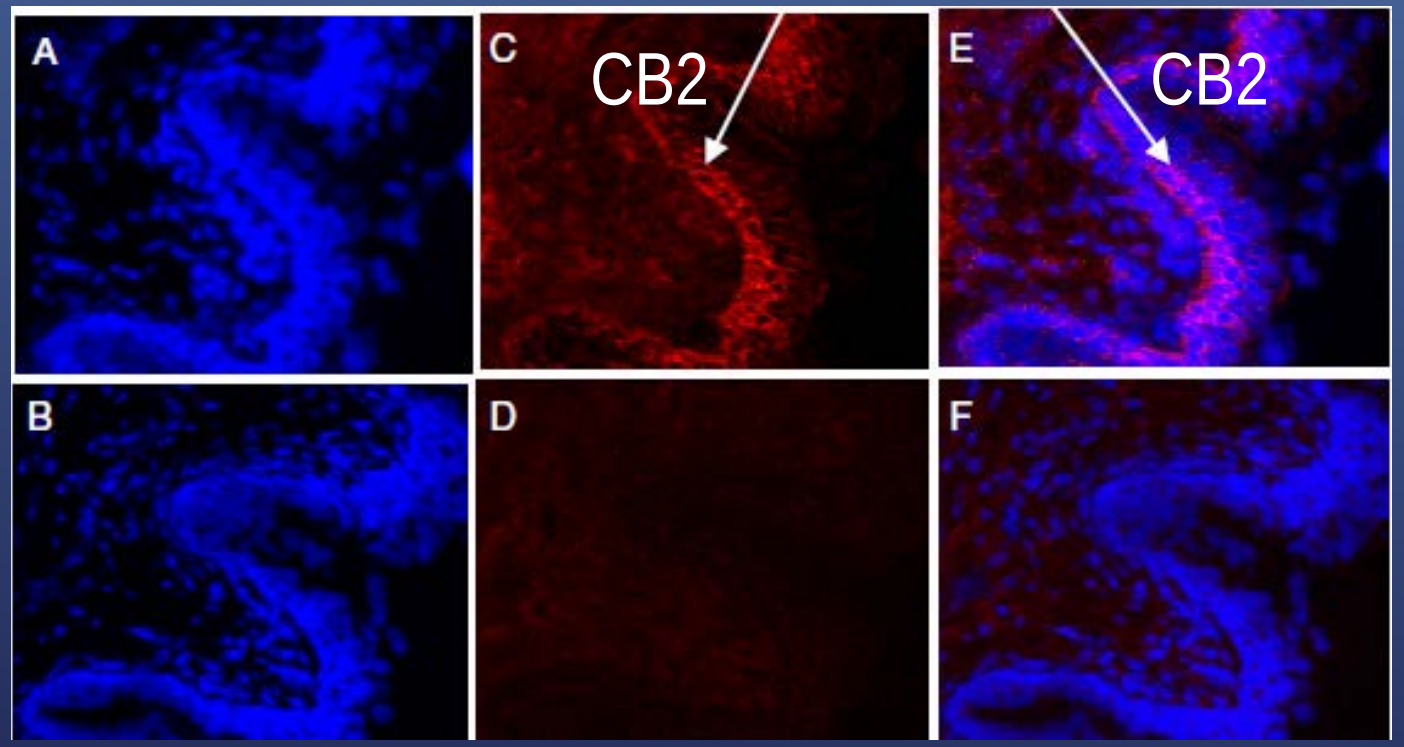
Targets and Drugs

- *Purinergic receptors - Antagonists*
- *Cannabinoid system - Agonists – Antagonists - Inhibitors*
- *TRP channels - Antagonists*

What is Promising?

Cannabinoid receptors – CB1 and CB2

CB2 receptors in the urothelium/lamina propria



Gratzke et al. J Urol , 2009;181:1939-1948

What is Promising?

Cannabinoid receptors - agonists

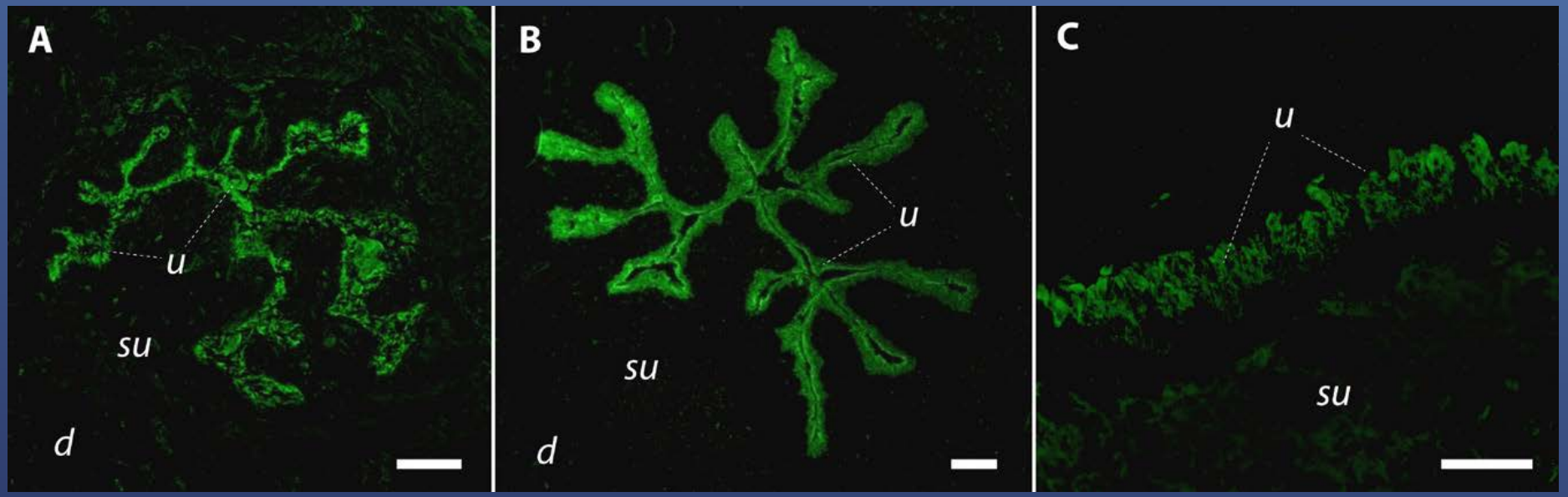
R. M. Freeman · O. Adekanmi · M. R. Waterfield ·
A. E. Waterfield · D. Wright · J. Zajicek

The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS)

Conclusion: The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS.

What is Promising?

Cannabinoids

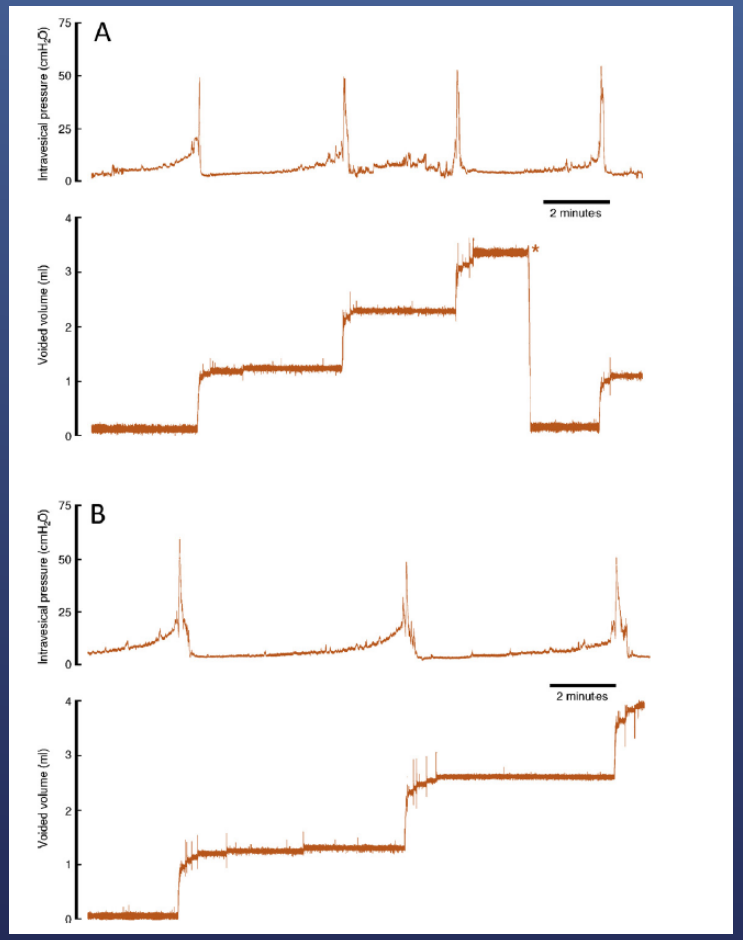


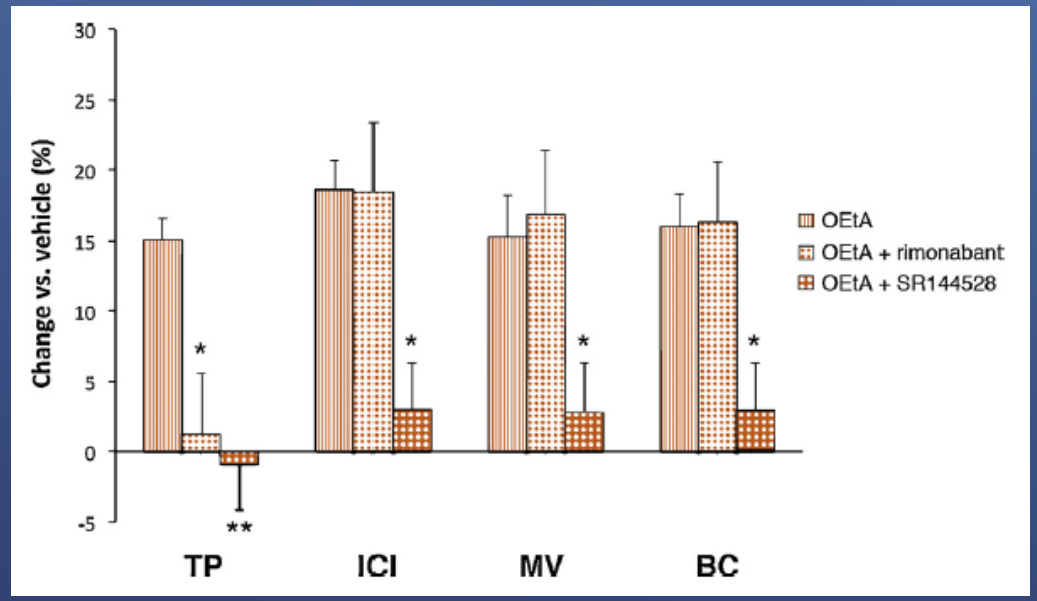
Distribution of fatty acid amide hydrolase (FAAH; cannabinoid degrading enzyme) immunoreactivity in the urothelium

Strittmatter et al., Eur Urol, 2012;61:98-106

What is Promising?

Effects of FAAH inhibition (OEtA) on rat cystometry





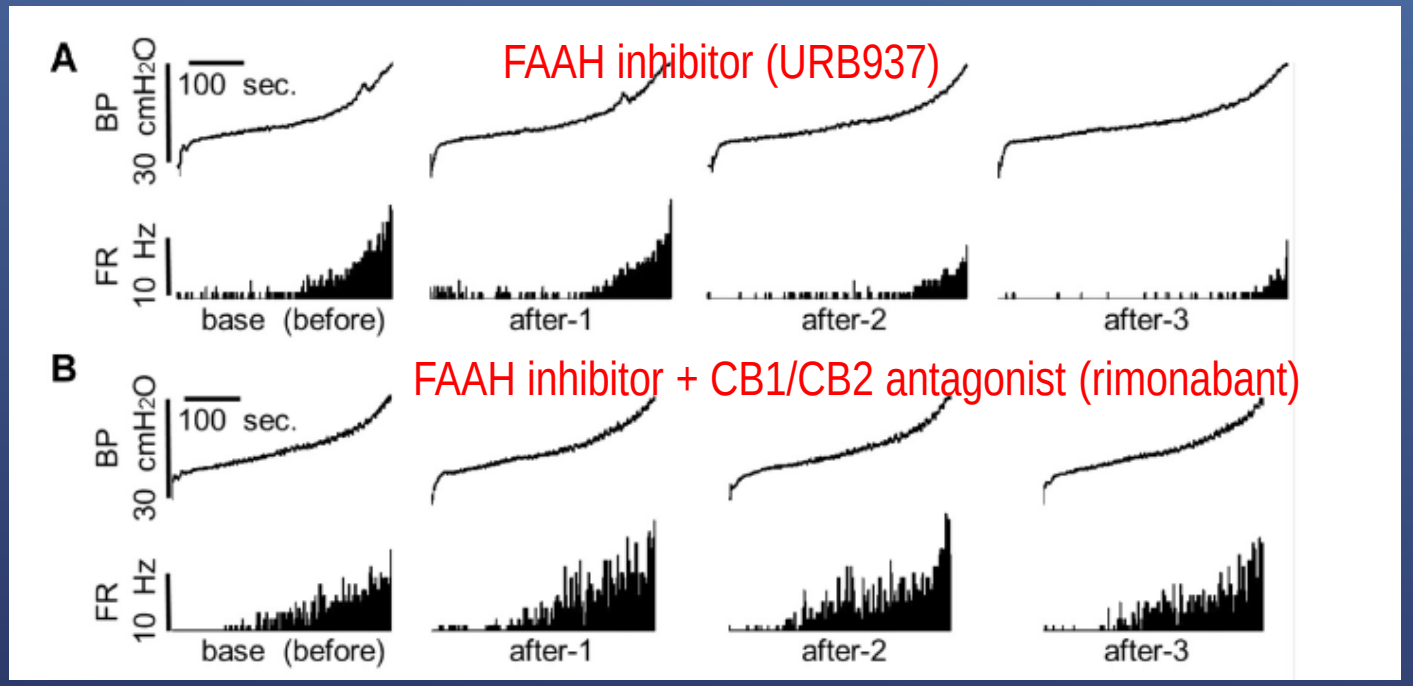
Rimonabant: CB1 receptor antagonist

SR144528: CB2 receptor antagonist

Strittmatter et al., Eur Urol, 2012;61:98-106

Inhibition of Peripheral FAAH Depresses Activities of Bladder Mechanosensitive Nerve Fibers of the Rat

Naoki Aizawa, Petter Hedlund,* Claudius Füllhase, Hiroki Ito, Yukio Hommat and Yasuhiko Igawa*,‡



”inhibiting peripheral FAAH depresses the Ad and C-fiber activity of primary bladder afferents via CB1 and CB2 receptors”

Aizawa et al, J Urol.., 2014 Sep;192(3):956-63

What is Promising?

The cannabinoid system

- Exocannabinoids:
  promising preliminary human data

- Endocannabinoids (FAAH inhibitors):
  promising animal data

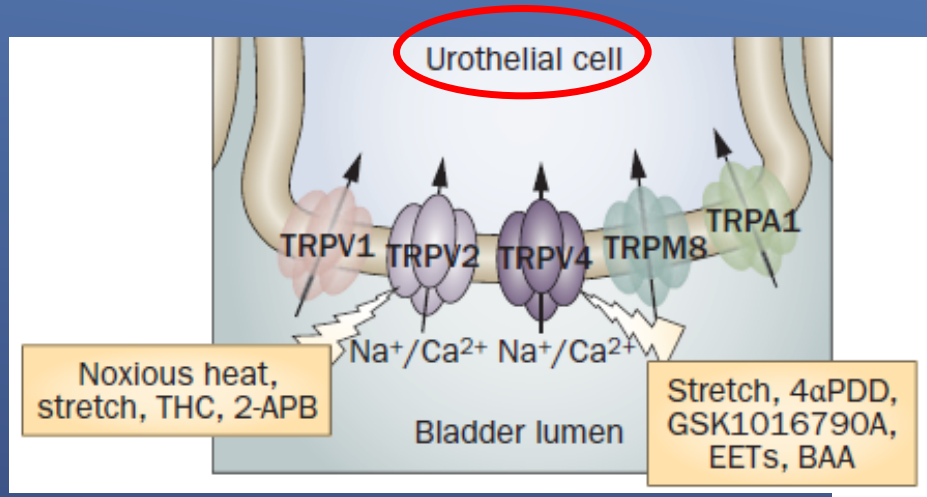
Potential for further development ?

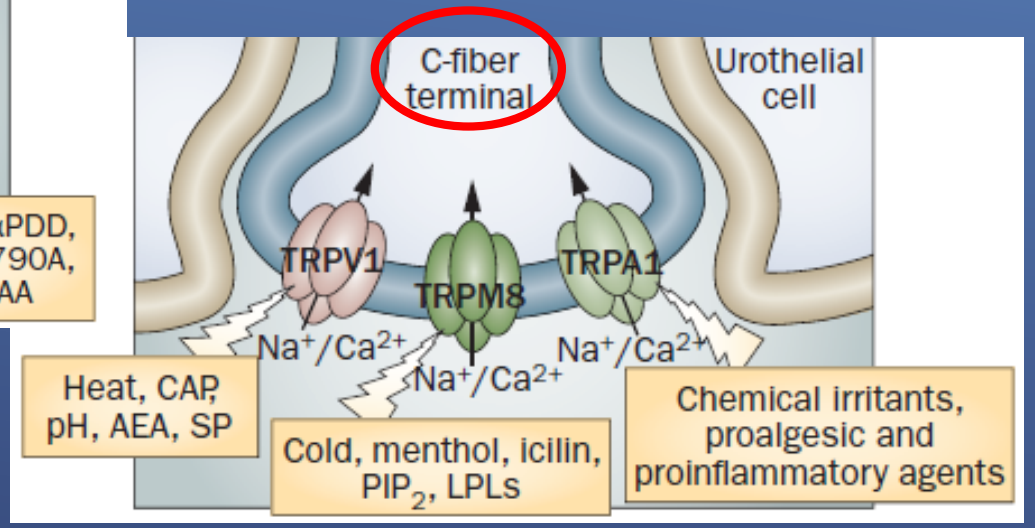
What is Promising?

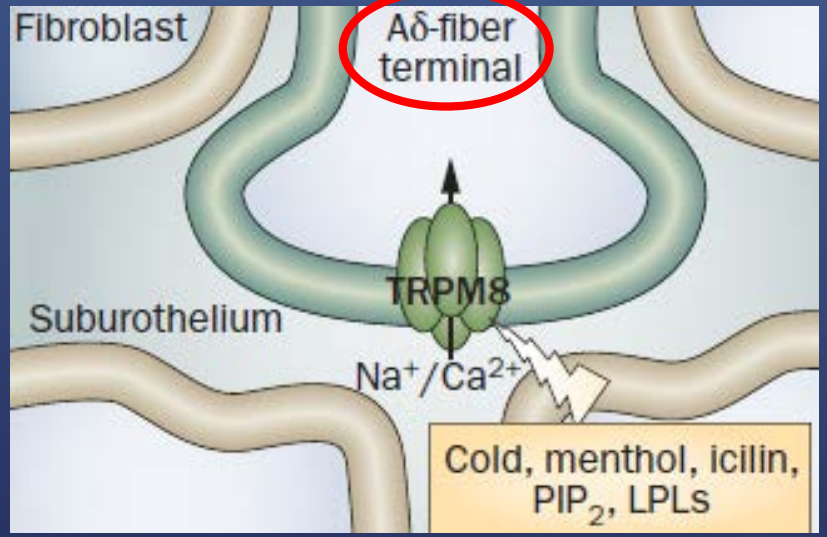
Targets and Drugs

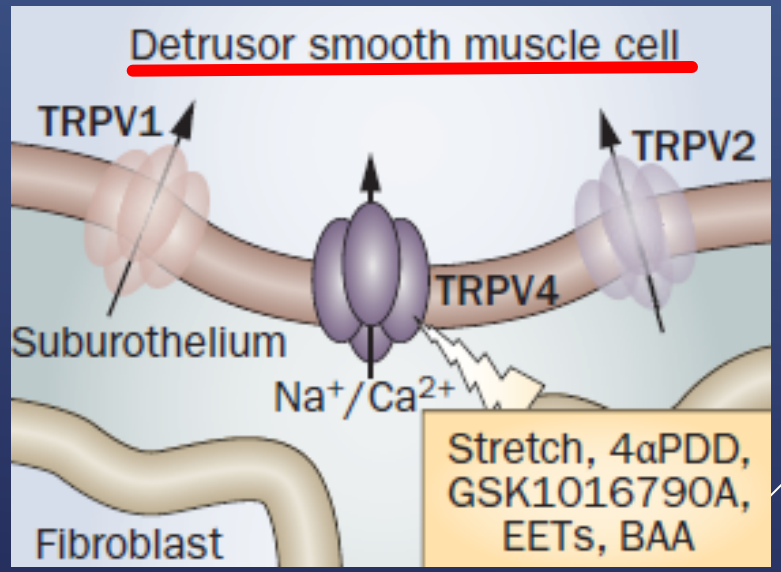
- *Purinergic receptors - Antagonists*
- *Cannabinoid system - Agonists – Antagonists - Inhibitors*
- *TRP channels - Antagonists*

TRP- Channels in the Bladder



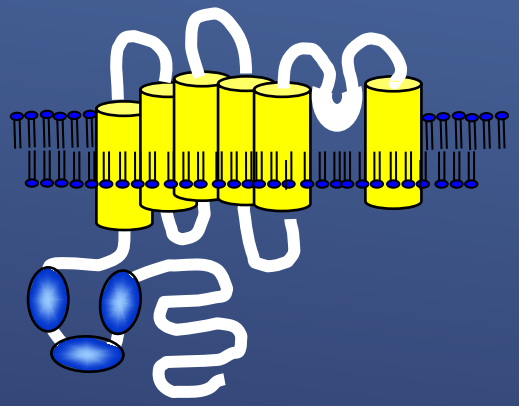




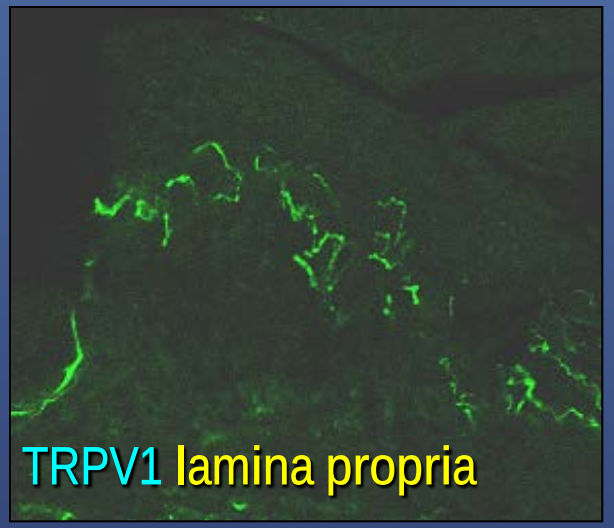


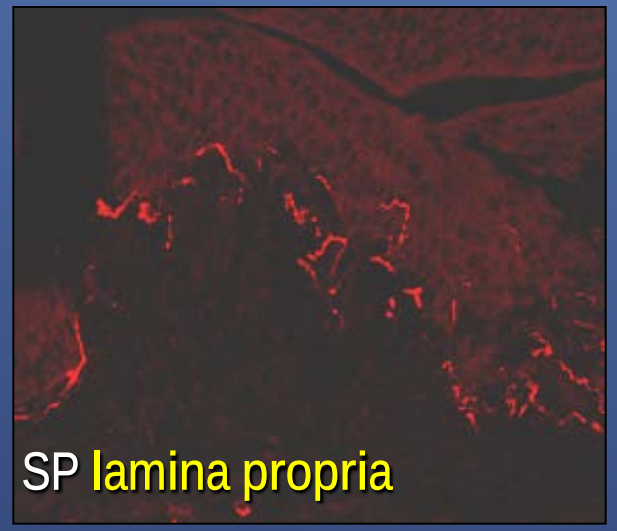
Skryma et al
Nat Rev Urol., 2011 Oct 4;8(11):617-30

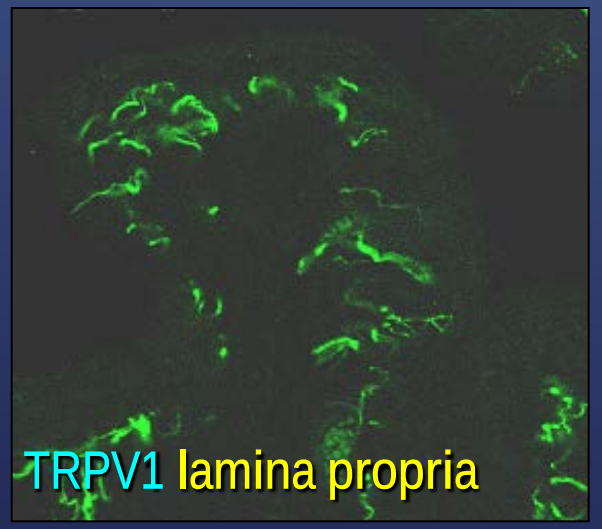
TRPV1 Receptors on Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) Containing Nerves in the Rat Bladder

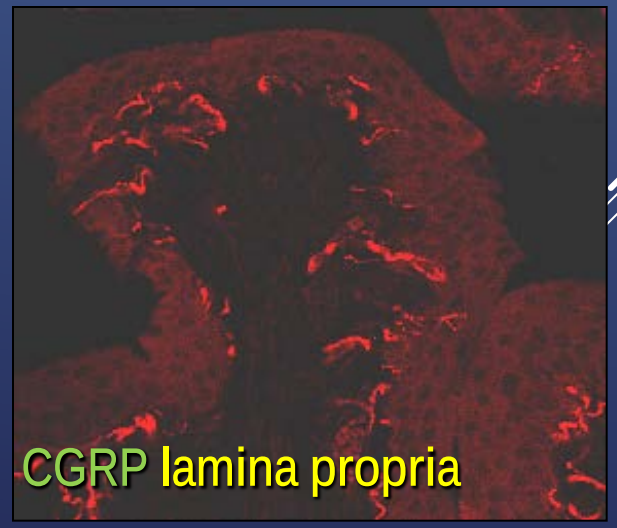


TRPV1



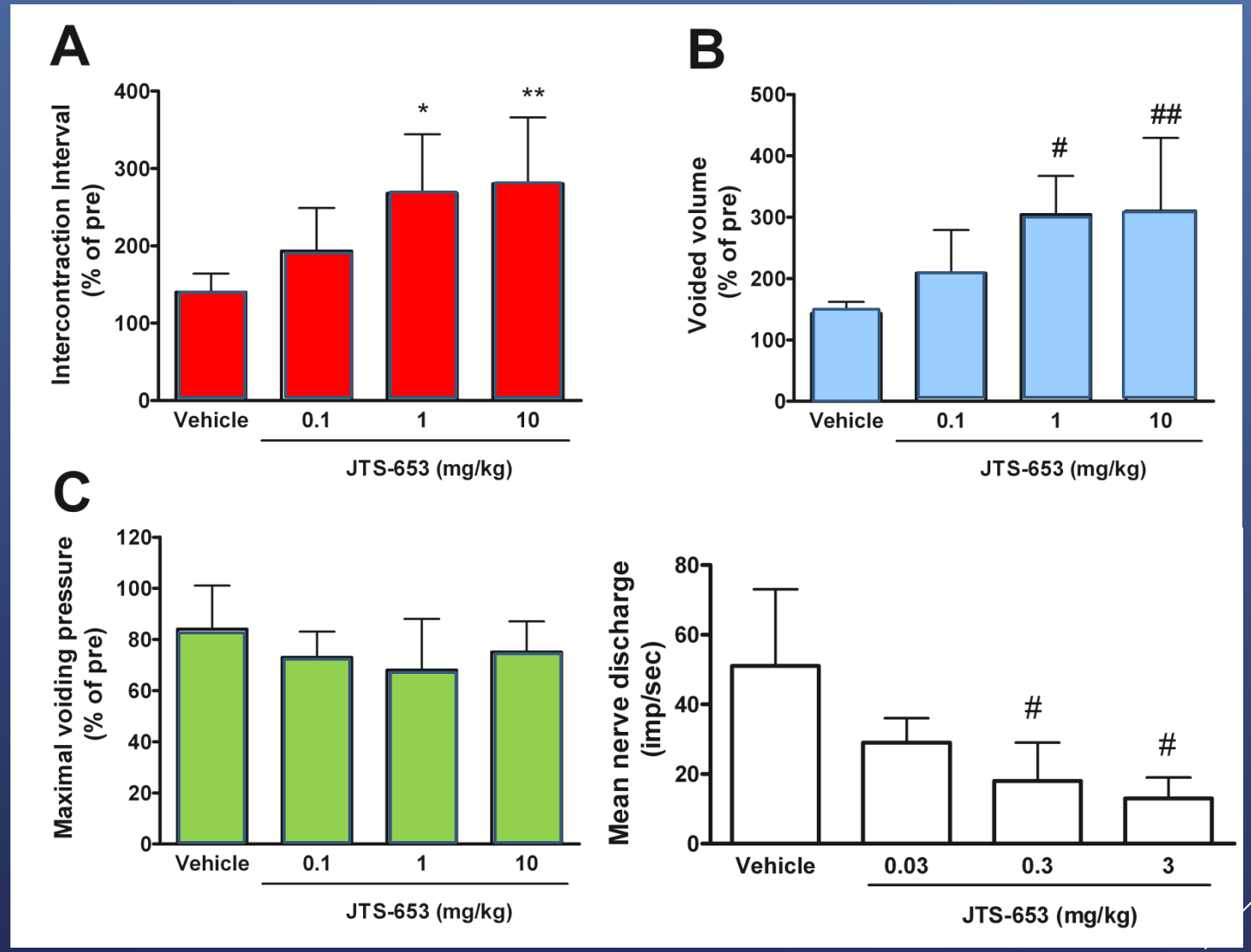






Avelino et al, Neuroscience 109(4):787, 2002

Effects of a Selective TRPV1 Antagonist on Rat bladder



Kitagawa et al., J Urol. 2013 Mar;189(3):1137-46

…:The observed increase in body temperature was not considered to be of clinical concern."

Br J Clin Pharmacol. 2011 Dec;72(6):921-31

Principles – Agents of Potential Interest

TRPV1 channel antagonists

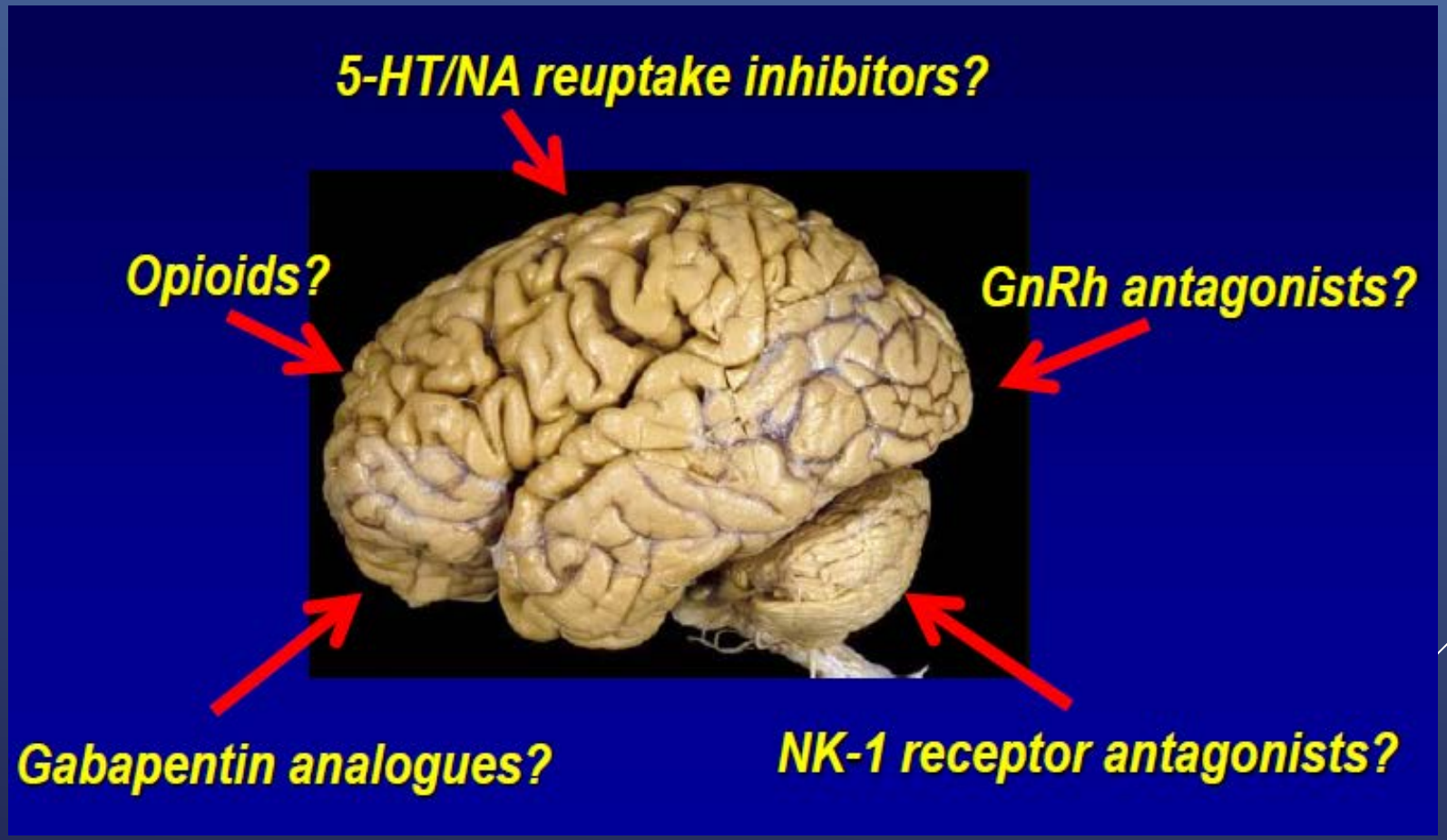
Promising animal data – but do they work in human OAB/DO?

Problems with side effects (hyperthermia)

Potential for further development

What is Promising?

Centrally acting drugs



Agents of Potential Interest: Limitations and Opportunities

Drugs with an action on the CNS

Several principles seem to work

Currently used drugs have low efficacy and/or unacceptable side effects

Great potential for further developments

How to Optimize Current OAB Treatment?

Individualized treatment

Combination therapy

Subcategorization of the OAB population (biomarkers?)

Progress and Opportunities for Pharmacological Treatments

Summary

Several unexplored targets

Promising animal data

Translation to clinic slow – no new drugs ready for clinical introduction

Combination therapy an alternative for improved effects