Progress and Opportunities for Pharmacological Treatments

Karl-Erik Andersson, MD, PhD

Wake Forest Institute for Regenerative Medicine,
Wake Forest University School of Medicine,
Winston Salem, North Carolina,
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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

- $\beta_3$–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
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 pathophysioses 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

- Increased afferent activity
- Decreased capacity to handle afferent information
- Decreased suprapontine inhibition
- Myogenic activity and influence of local factors
- Urothelial signaling
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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
Bladder Function in P2X3-deficient Mice

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

Anthony P. Ford
The Effect of a P2X3 Antagonist on Cystometric Reflexes in Anesthetized Rats

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

AF353 (1 mg/kg, i.v.)

Effects of AF-353 on Afferent Signaling from the Bladder

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

What is Promising?

Cannabinoid receptors - agonists

R. M. Freeman · O. Adelkanmi · 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 Mechnosensitive Nerve Fibers of the Rat

Naoki Aizawa, Petter Hedlund,* Claudius Fülhase, Hiroki Ito, Yukio Homma† 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
TRPV1 Receptors on Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) Containing Nerves in the Rat Bladder

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.”
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

5-HT/NA reuptake inhibitors?

Opioids?

GnRh antagonists?

Gabapentin analogues?

NK-1 receptor antagonists?
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?)
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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