Neural Control and Neuromodulation of Lower Urinary Tract Function

William C. de Groat
University of Pittsburgh
Topics

- Anatomy and functions of the lower urinary tract
- Peripheral innervation (efferent and afferent nerves)
- Central neural control of the lower urinary tract
- Lower urinary tract dysfunction
- Treatment of dysfunction (neuromodulation)
- Research opportunities
Anatomy and Functions of the Lower Urinary Tract

Functions

1. Urine storage
   - Reservoir: Bladder
2. Urine release
   - Outlet: Urethra

Two Types of Voiding

INVOLUNTARY (Reflex)
- (infant & fetus)
  Defect in Maturation

VOLUNTARY
- (adult)

THERAPY

Parkinson’s, MS, stroke, brain tumors, spinal cord injury, aging, cystitis
Lower Urinary Tract Innervation
Two Types of Visceral Afferent Neurons: Bladder & Bowel
Aδ-fibers responsible for normal bladder sensations
C-fibers contribute to urgency, frequency and incontinence
Afferent Sensitivity may be Influenced by Substances Released from the Urothelium

CNS

Aδ fiber

C fiber

Urothelium
The Bladder Urothelium

- Glycosaminoglycan Layer
- Uroplakin Plaques and Discoidal Vesicles
- Zonula Occludens

- Umbrella Cell Stratum
- Intermediate Cell Stratum
- Basal Cell Stratum

Afferent Nerve fiber
Urothelial-Afferent Interactions

ATP, NO, NKA, ACh, NGF

Capsaicin, temperature, H⁺, stretch

nAChR

mAChR

P2X

P2Y

NK2

TrKA

NGF

TRPs

ATP, ACh

Afferent nerves

Efferent nerves

Urothelium

Myofibroblast

Detrusor smooth muscle

Afferent nerves

Efferent nerves

Myofibroblast
Interaction of Sensory Pathways of Multiple Pelvic Organs

Convergent

Dichotomizing

Branch point
Somatic and Visceral Afferent Convergence: Contribution to Visceral Referred Pain
Micturition Switching Circuit

- Bladder
- Low level afferent activity
- Elimination
- OFF
- Storage
- ON
- Urethral Sphincter
- CNS Switch
Micturition Switching Circuit

Bladder Distension

High level afferent activity

Elimination

ON

Storage

OFF

CNS Switch

Urethral Sphincter
Voluntary Control of Voiding

Sensation of Bladder Filling

Prepared by C. J. Fowler
Voluntary Control of Voiding

Sensation of Bladder Filling

thinly myelinated Aδ
Inhibition of the Periaqueductal Gray (PAG) and Pontine Micturition Center (PMC) by the Forebrain Promotes Urine Storage
Excitatory Signals from the Forebrain Elicits Voluntary Voiding
Voiding

Coordinated Bladder Contraction and Urethral Sphincter Relaxation

PMC

S2-4 in cauda equina

pelvic & pudendal nerves
Forebrain Circuitry Controlling Voiding

W. C. de Groat et. al., 2015 Comp Physiology
Pathophysiology of OAB

Dysfunction of the detrusor or neural pathways alters the balance of inhibitory and excitatory stimuli critical to voluntary bladder control.

1. Phasic smooth muscle contractions
2. Activation of sensory nerves
3. Enhanced excitatory transmission in the CNS
4. Reduced CNS inhibition

References: 1. Fowler CJ.
Neuromodulation of the Micturition Switch

Bladder

High level afferent activity

Elimination

OFF

Storage

ON

CNS Switch

Urethral Sphincter

Afferent Nerve Stimulation: Tibial, Pudendal, Sacral Roots, Skin, Vagina, Urethra, Penis
Sacral Neuromodulation

1. FDA-approved therapy:
   - urinary urge incontinence
   - urinary urgency-frequency
   - non-obstructive urinary retention
   - fecal incontinence

2. Experimental:
   - interstitial cystitis
   - pelvic pain
Release of neurotransmitters, activation of receptors and modulation of CNS function

Activation of afferent axons sends signals to the CNS

Stimulation of Sacral Spinal Nerve Root

To brain stem

Dorsal column

Dorsal root ganglion neuron

Stimulation ofSacral Spinal Nerve Root
Sites of Stimulation

Sacral (S3)

Tibial Nerve

Pudendal Nerve
Questions about Neuromodulation

- What types of axons are activated?
- What neurotransmitters are released?
- What neurotransmitter receptors are activated?
- Where does the neuromodulation occur (Urinary bladder, Peripheral nervous system, Spinal cord, Brain, CNS sensory or motor pathways?)
- Do different types of neuromodulation act by the same mechanism?
Pudendal Neuromodulation (PNS)

*Site of Action:* Spinal cord

*Mechanisms:* Activation of GABAergic Inhibition and activation of hypogastric inhibitory pathway to the bladder

*Properties:* Stimulation is effective over a narrow range of frequencies (3-10 Hz) and effects require continuous stimulation.

(Xiao, Z., et.al., AJP Renal, 306: F-381, 2014)
Tibial Neuromodulation (TNS)

**Site of Action:** Brain Stem

**Mechanisms:** Activation of opioid receptors and enkephalinergic inhibition.

**Properties:** Stimulation effective over a wide range of frequencies (3-30 Hz) and persists for at least two hours after the termination of stimulation.

**FDA approved:** 30 min therapy administered every week for 12 weeks and then booster treatments once a month.

(Matsuta, Y et.al., AJP Reg., 305:R126, 2013)
• Initial bladder areflexia and loss of voluntary control

• Later development of automatic micturition

• Bladder hyperreflexia or autonomous detrusor hyperactivity

• Unmasking of a primitive neonatal bladder reflex

• Loss of bladder sphincter coordination (Detrusor-Sphincter-Dyssynergia)

• Thus after neural injury the bladder doesn’t store well or empty well
Bladder Sphincter Coordination: Effect of Spinal Cord Injury

ADULT

BLADDER PRESSURE

VOLUNTARY VOID

START

STOP

START

PARAPLEGIC

BLADDER PRESSURE

REFLEX VOID

BLADDER-SPHINCTER DYSSYNERGIA

BLADDER FILLING

BLADDER FILLING

EMG
Emergence of C-Fiber Micturition Reflex After Chronic Spinal Cord Transection

- Cortical diencephalic mechanisms
- (+ -) Brainstem switch
- Spinal tract neurons
- Spinal efferent mechanisms
- Myelinated afferents
- Capsaicin block
- Unmyelinated afferents
- Cold stimulation excites
- Ganglia
- Detrusor
Pudendal Neuromodulation of the LUT After Spinal Cord Injury in Cats

SCI 6 - 12 months

Sacral Cord

Pudendal N.

Electrical Stimulation at 0.5 – 40 Hz
(At low Hz inhibits reflex bladder contractions
and at higher Hz induces reflex contractions)

(Tai, C., et.al., Neurourol Urodynam, 26:879, 2007)
Research Opportunities

• Mechanisms of prolonged effects of neuromodulation (NM).
• Transmitters mediating clinical effects of NM.
• Test drug-NM combination therapies.
• Test a combination of sphincter motor axon block and reflex bladder activation to promote voiding after spinal cord injury.
• Determine if different types of neuromodulation act by similar mechanisms.
• Examine the effects of sympathetic nerve stimulation on LUT.
• Examine possible synergistic interactions between NM evoked by stimulation at different sites.
• Examine the mechanisms of urothelial-afferent interactions.
• Examine the function of intramural reflexes in the bladder.
• Examine the physiological functions of dichotomizing afferents.
• Study pelvic organ function with optogenetics methods.
Fig 8

**Pudendal Nerve**

- **PAG-PMC**
- **MTEP site of action**
- **Excitatory neuron**
- **Excitatory synapse**
- **Inhibitory neuron**
- **Inhibitory synapse**

- **Aδ-fiber**
- **C-fiber**

- **Bladder**
- **EUS**

**Sacral Cord**

**Pelvic Nerve**

**Pudendal Nerve**
**Fig 9**

Tibial Nerve

PAG-PMC

- MTEP site of action
- Excitatory neuron
- Excitatory synapse
- Inhibitory neuron
- Inhibitory synapse

- Aδ-fiber
- C-fiber

- Tibial Nerve
- Sacral Cord
- Pelvic Nerve
- Bladder
- EUS
Fig 6

Circuit 1
- Insula
- IPFC
- Desire to Void

Circuit 2
- SMA/dACC
- th
- Urethra, pelvic floor

Circuit 3
- Parahippocampal
- PAG
- PMC
- Parasympathetic
- Voiding Reflex

Bladder
- Urethra
- ON
- Sa
- Voiding Reflex