Neural Control of Lower Urinary Tract Function

William C. de Groat
University of Pittsburgh Medical School
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Topics

- Lower urinary tract: functions, anatomy and innervation.
- Properties of bladder afferent nerves
- Central neural control of voiding
- Mechanisms underlying urine storage and voiding dysfunction
Functions of the Lower Urinary Tract

- Urine storage in a reservoir (bladder)
- Urine release through an outlet (urethra)
- Both functions controlled by circuitry in the central nervous system.
- Neural circuitry acts like a switch to turn micturition off and on.
- Micturition requires the coordination of smooth and striated muscle.
Lower Urinary Tract Innervation

Reservoir

- Bladder (parasympathetic)
  - M3 receptor (+)
  - NA

- Bladder (somatic)
  - α1 receptor (+)
  - NA

- Urethral smooth muscle
  - β3 receptor (-)

- Urethra
  - Nicotinic receptor (+)

- Detrusor muscle

- Pudendal nerve (somatic)
  - Urogenital diaphragm
  - ACh

- Pelvic nerve (sympathetic)
  - Hypogastric nerve fibers
  - NA

- Parasympathetic
  - Bladder (parasympathetic)
  - NA

- Sympathetic
  - Bladder (sympathetic)
  - NA

- Somatic
  - Striated muscle of pelvic floor
  - Striated urethral sphincter

- Cerebral cortex
  - Pontine micturition center

- Thoracic region
  - Hypogastric nerve fibers

- Lumbar region
  - Pelvic nerve fibers

- Sacral region
  - Sacral nerve fibers

Urethral Outlet
TYPES OF VOIDING

INVOLUNTARY (Reflex) (infant & fetus)

Maturation

Defect in Maturation

THERAPY

INVOLUNTARY (Reflex) (adult)

VOLUNTARY (adult)

Parkinson’s, MS, stroke, brain tumors, spinal cord injury, aging, cystitis
Micturition Switching Circuit

Bladder

Low level afferent activity

Elimination

OFF

Storage

ON

CNS Switch

Urethral Sphincter
Bladder Distension

High level afferent activity

Elimination

ON

Storage

OFF

CNS Switch

Urethral Sphincter

Micturition Switching Circuit
Two Types of Bladder Afferents

- **A-fiber type**: small myelinated axons that respond to bladder distension and trigger sensation of bladder fullness and desire to void.

- **C-fiber type**: unmyelinated axons that do not respond to bladder distension but do respond to noxious stimuli. These afferents trigger painful sensations and may be responsible for urgency and urge incontinence.
Healthy: Empty Bladder

URINARY BLADDER

Aδ-Fiber

C-Fiber
Healthy: Bladder Distension

Aδ-Fiber

C-Fiber

ON

Mechano-sensitive Aδ afferents
Mechano-insensitive C-fiber afferents

Input
Silent

URINARY BLADDER
Reflexes Evoked by Aδ Afferents in the Pelvic Nerve

Spinal Storage Reflexes

Supraspinal Voiding Reflexes

Pathology: Bladder Distension

Pathology alters the properties of C-fiber afferents inducing mechano-sensitivity.

OAB Bladder
Urgency
Incontinence
Pain
Central Pathways Activated by C-Fiber Afferents

Brain/PAG/PMC

PMC = Pontine micturition center
PAG = Periaqueductal grey

1 = Primary afferent neuron
2 = Spinal tract neuron
3 = Excitatory interneuron
4 = Parasympathetic preganglionic Neuron

1 = Primary afferent neuron
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Neuronal subtypes in the pontine micturition center of the cat

A DIRECT NEURON

B INVERSE NEURON

C INDEPENDENT NEURON

Similar subtypes are present in the PAG

Contractions recorded in a distended bladder under isovolumetric conditions
Distribution of Different Types of Bladder Neurons in the Rostral Pons

<table>
<thead>
<tr>
<th>Type of Neuron</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Neurons</td>
<td>35</td>
<td>20.7</td>
</tr>
<tr>
<td>Inverse Neurons</td>
<td>86</td>
<td>50.9</td>
</tr>
<tr>
<td>On-Off Neurons</td>
<td>6</td>
<td>3.6</td>
</tr>
<tr>
<td>Independent Neurons</td>
<td>42</td>
<td>24.9*</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>100.0</td>
</tr>
</tbody>
</table>

de Groat, W., et. al., Behav Brain Res, 1998;
**Excitatory Circuit**

Circuit #1

- **Pons**
  - Direct neuron

- **Periaqueductal gray**
  - E

- **Spinal cord**
  - E
  - Sensory neuron

- **Bladder**

**Full Bladder**

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

*de Groat & Wickens, 2013*
Feed-forward Inhibitory Circuit

Circuit #2

Partially filled bladder

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

d de Groat & Wickens, 2013
Combined Excitatory and Inhibitory Circuits

Circuits #1 & #2
**During Storage**

**Tonically Active Inhibitory Neurons** Suppress the Excitatory Circuit
Voiding is initiated by increased afferent excitatory input which overcomes tonic inhibition and turns off the inhibitory circuit.
8 Types of neurons can create an “on-off switch”

The “switch” requires mutual inhibition and tonically active inhibitory neurons
Neurotransmitters

Inhibitory:
  - GABA
  - Opioid peptides

Excitatory:
  - Glutamate

Storage

Tonically active independent neuron

Pons

Periaqueductal gray

Spinal cord

Sensory neuron

Bladder

Empty Bladder

Cystometry
L3-L4 spinal cord is also involved in bladder and sphincter function

This region of the spinal cord has been ignored until recently because it does not contain autonomic neurons that innervate the bladder or motoneurons that innervate the urethral sphincter.
L3-L4 spinal cord contains a lumbar spinal coordinating center (LSCC)

Electrical stimulation in these segments induces phasic sphincter activity in rats

After spinal injury in rats L3-L4 lumbar spinal mechanisms are essential for coordinating bladder and sphincter activity.

Chang, H. et al., AJP Renal 2007
L3-L4 spinal cord contains a lumbar spinal coordinating center (LSCC)

These segments of the cord also contain the central pattern generator for locomotion. Thus electrical epidural stimulation was applied in this region to improve motor function in spinal cord injured patients.

Unexpectedly bladder function including voluntary voiding and bladder sensation also improved. (Harkema et al., 2015)
Pseudorabies Virus (PRV) Transneuronal Tracing

LSCC

Central Canal

L3:

PRV-RFP

EUS

PRV-GFP

Bladder

L6:

DCM

EUS-MN

RFP: Red Fluorescent Protein
GFP: Green Fluorescent Protein
Transverse slice of the spinal cord (P20-P24)

Bridge is in the region of the dorsal commissure

Bridge

gray matter area containing LSCC neurons

Wings
Horizontal L4-L3 sections at CC level in two different rats (both P65) with clouds of viral infection.

100-150 nl of AAV-GFP injected in L3 around CC spread for up to 500 μm in the neuropil.

PRV614-RFP in EUS reveals EUS-related propriospinal neurons in L3-L4.
PRV-RFP Labelling in L6 spinal cord

LSCC

Neurons infected with AAV-GFP in L3-L4 project their axons down into L6-S1. Dense axonal ramification within Onuf’s nucleus suggests synaptic contacts with motoneurons.

PRV614-RFP in EUS reveals EUS-related propriospinal neurons in L3-L4
Circuit 1

- Insula
- IPFC
- Desire to void

Circuit 2

- SMA/dACC
- th
- Urethra, pelvic floor

Circuit 3

- Parahippocampal
- PAG
- PMC
- Parasympathetic
- Sa
- ON
- Urethra

Voiding reflex

LSCC

de Groat, Griffiths & Yoshimura, 2015
Conclusions

- The etiology of OAB is uncertain but may be neurogenic, myogenic, or both

- Neurogenic theory
  - Reduced pontine or suprapontine inhibition
  - Damaged axonal paths in the spinal cord and/or brain
  - Increased primary afferent input
  - Loss of peripheral or spinal inhibition
  - Enhanced excitatory neurotransmission in the micturition reflex pathway

- Myogenic theory

- Excitability
- Electrical coupling between myocytes
- Propagation of coordinated contractions
Spinal And Supraspinal EUS Reflex Mechanisms

Spinal Bursting Mechanism in the L3-L4 Spinal Cord

Chang, H., et al., AJP Renal 2007
Excitatory Circuit

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

de Groat & Wickens, 2013