Lower Urinary Tract Dysfunction After Spinal Cord Injury: Pathophysiology and the Development of New Therapies
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Topics

• Introduction: review of the neural control of the lower urinary tract.
• Changes in lower urinary tract function after spinal cord injury (SCI).
• Plasticity in bladder afferent pathways after SCI and role of neurotrophic factors.
• Treatment of neurogenic lower urinary tract dysfunction using neuromodulation.
Functions of the Lower Urinary Tract

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

INVOLUNTARY (Reflex) (infant & fetus)

Defect in Maturation

Maturation

THERAPY

INVOLUNTARY (Reflex) (adult)

VOLUNTARY (adult)

Parkinson’s, MS, stroke, brain tumors, spinal cord injury, aging, cystitis
Reflex Control of Lower Urinary Tract

Bladder

Low level afferent activity

Elimination

Storage

CNS Switch

Urethral Sphincter
Reflex Control of Lower Urinary Tract

Bladder Distension → High level afferent activity → Elimination → ON → Storage → OFF → CNS Switch

- Urethral Sphincter
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

S2-4 roots in cauda equina

pelvic & pudendal nerves
• Initial bladder areflexia and loss of voluntary control

• Later development of automatic micturition

• Emergence of bladder hyperreflexia or autonomous detrusor hyperactivity

• Unmasking of a primitive neonatal bladder reflex

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

• After spinal injury the bladder doesn’t store well or empty well
Cystometry and Urethral Sphincter EMG
Spinal Micturition Circuit and DSD

- **Bladder Distension**
- **High level afferent activity**
- **Elimination**
- **Spinal Switch**
- **Storage**
- **Sphincter Contraction**
- **Inefficient Voiding**
- **DSD**
Questions?

• What are the mechanisms that underlie the development of neurogenic detrusor overactivity and detrusor-sphincter-dyssynergia?

• How can efficient urine storage and voiding functions be restored after SCI?
The bladder is innervated by two types of afferents. Voluntary control of voiding is dependent on A-δ afferents and a supraspinal micturition reflex pathway.
Voluntary voiding and supraspinal micturition reflex mediated by mechano-sensitive A-δ afferents.

Unmyelinated afferents are unresponsive to bladder distension (i.e., mechano-insensitive)
Spinal injury unmasks a reflex mediated by C-fiber afferents which become mechano-sensitive in pathological conditions.
Spinal micturition reflex is mediated by C-fiber afferents in pathological conditions.

Spinal cord injury

Unmyelinated afferents (C)

Spinal Efferent Mechanisms

Ganglia

Detrusor

Cortical Diencephalic Mechanisms

Brain Stem Switch
Changes in Bladder Reflex Pathways after Spinal Cord Injury (Neuroplasticity)

1. Plasticity in Bladder Afferent Pathways

2. Remodeling of pathways in the spinal cord
Spinal Intact: Empty Bladder

A\textsuperscript{\textdelta}-Fiber

C-Fiber

URINARY BLADDER
Spinal Intact: Distension

URINARY BLADDER

ON

Aδ -Fiber

C-Fiber

Input

Silent
Spinal Intact: Distension

Input

A\(\delta\) - Fiber

C-Fiber

ON

Mechano-sensitive A\(\delta\) afferents

Mechano-insensitive C-fiber afferents

Silent

URINARY BLADDER
Spinal Cord Injury: Distension

After spinal cord injury, C-fiber afferents become mechano-sensitive.

Distension

Aδ -Fiber

C-Fiber

Input

Bladder Hyperreflexia
Incontinence
DSD
Question

How Does Spinal Cord Injury Induce Neuroplasticity and Change the Properties of C-Fiber Bladder Afferent Neurons?
Spinal cord injury (SCI) induces detrusor-sphincter-dyssynergia leading to urethral outlet obstruction and urinary retention.

Urinary retention leads to bladder overdistension and bladder hypertrophy (Rodent model)

Bladder hypertrophy is accompanied by hypertrophy of afferent and efferent neurons that innervate the bladder.

Diversion of urine into the intestine in SCI rats prevents bladder distension and eliminates bladder and neuronal hypertrophy.
Mechanisms of Neuroplasticity

- Nerve growth factor (NGF) increases in the bladder and spinal cord after SCI.
- NGF stimulates axonal growth and changes the properties of C-fiber bladder afferents.
1. Spinal cord injury

2. Striated sphincter dyssynergia

3. Bladder hypertrophy

4. NGF expression

5. NGF transport

6. Bladder afferent neurons
   - ↑ cell size
   - ↑ excitability
   - ↑ transmitter expression
   - ↑ receptor expression

7. Bladder hyperreflexia and ↑ DSD

Bladder Afferent Neuron Plasticity After Spinal Cord Injury
Afferent Axonal Sprouting in the Spinal Cord After SCI

**Spinal Intact (VIP-IR Afferent Axons)**

**Chronic Spinal (HRP-labeled and VIP-IR Afferent Axons)**
Effects of exogenous NGF are similar to the effects of SCI

1. NGF injected intrathecally or into the bladder wall

2. NGF levels ↑

3. NGF transport

4. bladder afferent neurons
   - cell size ↑
   - K+ channel function ↓
   - excitability ↑

5. Bladder hyperreflexia
1. Spinal cord injury

6. Bladder afferent neurons
   - cell size ↑
   - neurofilament ↑
   - excitability ↑

7. Bladder hyperreflexia

2. Striated sphincter dyssynergia

Decrease NGF levels

Immuno-neutralization of NGF
Treatments for LUT Dysfunctions after SCI

Goals:

1. Improve urine storage by suppressing neurogenic detrusor overactivity and reducing baseline intravesical pressure.

2. Improve voiding efficiency by enhancing the amplitude and/or durations of bladder contractions.

3. Improve voiding efficiency by suppressing detrusor-sphincter dyssynergia and enhancing detrusor-sphincter coordination.
Therapies for SCI-Induced Lower Urinary Tract Dysfunction

- Antimuscarinics
- BoNTA
- Resiniferatoxin
- Na$^+$ channel blockers
- NGF antibodies?
- Neuromodulation
- Bladder reinnervation

Central processing

Lower Urinary Tract Dysfunction

S$^2$-S$^4$

Sensory activation

Bladder distension

EUS

Experimental
Therapies for SCI-Induced Lower Urinary Tract Dysfunction

Antimuscarinics
BoNTA
Resiniferatoxin
Na$^+$ channel blockers
NGF antibodies?
Neuromodulation
Bladder reinnervation

Central processing

Lower Urinary Tract Dysfunction

Sensory activation

EUS Contraction

Bladder Contraction

Experimental
Therapies for SCI-Induced Lower Urinary Tract Dysfunction

Antimuscarinics
BoNTA
Resiniferatoxin
Na⁺ channel blockers
NGF antibodies?
Neuromodulation
Bladder reinnervation

Central processing

Experimental

Neuromodulation

Lower Urinary Tract Dysfunction

Bladder Contraction

EUS Contraction

S₂-S₄

Sensory activation
Types of Neuromodulation

1. Sacral anterior root stimulation
2. Sacral spinal root stimulation
3. Pudendal nerve stimulation
4. Tibial nerve stimulation
5. Dorsal genital nerve stimulation
6. Epidural stimulation
Types of Neuromodulation

1. Sacral anterior root stimulation
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Sacral Anterior Root Stimulation (Brindley Method)

- **Bladder Pressure**
- **Elimination**
- **Sphincter Relaxation**
- **Voiding**
- **Section Sacral Dorsal Roots**
- **Spinal Switch**
- **STIM ON**
- **STIM OFF**
- **Storage OFF**
Types of Neuromodulation

1. Sacral anterior root stimulation
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5. Dorsal genital nerve stimulation
6. Epidural stimulation
Sacral Neuromodulation

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

2. Experimental:
   interstitial cystitis, pelvic pain,
Sacral Neuromodulation

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

2. Experimental:
   interstitial cystitis, pelvic pain,

Not FDA approved for treating neurogenic bladder dysfunction after spinal cord injury
Early Sacral Neuromodulation Prevents Urinary Incontinence After Complete Spinal Cord Injury

Karl-Dietrich Sievert, MD,1 Bastian Amend, MD,1 G. Gakis, MD,1 P. Toomey,1 A. Badke, MD,2 H.P. Kaps, MD,2 and Arnulf Stenzl, MD1

Background: The study aim was to investigate potential influences on human nerves and pelvic organs through early implantation of bilateral sacral nerve modulators (SNMs) in complete spinal cord injury (SCI) patients during the acute bladder-areflexia phase.

Methods: Ten patients with neurologically-confirmed complete spinal cord lesions (SCLs) were provided with bilateral SNMs during the phase of atonic-detrusor muscle. Modulation was achieved by two electrodes implanted into each S3-foramen. Six patients declined and served as controls. The mean follow-up was 26.2 months.

Results: Videourodynamics (VU) confirmed detrusor acontractility, resulting in urinary continence as well as significant reductions in urinary tract infections (UTIs). Bowel movements did not require oral laxatives; additional preprogrammed parameters achieved erections for intercourse.

Interpretation: Early SNM implantation in SCI patients may revolutionize neurogenic lower urinary tract (LUT) dysfunction management; it prevented detrusor overactivity and urinary incontinence, ensured normal bladder capacity, reduced UTI rates, and improved bowel and erectile functionality without nerve damage.

Conclusion: Future SCI investigations will be conducted to evaluate the potential benefits of even earlier SNM placement to progressively enhance pelvic organ functionality. This new approach may provide important clues required for assessing whether neuronal information is passed through the sympathetic trunk ganglion to the brain after complete SCI. Further investigations are needed to determine if functional magnetic resonance imaging (fMRI) might be helpful for analyzing changes in brain function in patients with SNMs and those taking antimuscarinics.

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Sacral Neuromodulation: stimulation of afferent axons releases neurotransmitters which activate receptors and modulate CNS function.
Sites of Stimulation

Sacral (S3)
Tibial Nerve
Pudendal Nerve
Types of Neuromodulation

1. Sacral anterior root stimulation
2. Sacral spinal root stimulation
3. Pudendal nerve stimulation
4. Tibial nerve stimulation
5. Dorsal genital nerve stimulation
6. Epidural stimulation
Pudendal Afferents Innervate Multiple Targets

1. Urethral and anal striated sphincters
2. Urethral and anal mucosa
3. Penis and clitoris
4. Vagina and uterine cervix
5. Cutaneous and subcutaneous tissues in the perineum
Pudendal Afferents Innervate Multiple Targets

1. Urethral and anal striated sphincters
2. Urethral and anal mucosa
3. Penis, clitoris, vagina and uterine cervix

Thus not unexpected that pudendal nerve stimulation has complex effects on lower urinary tract function.
Multiple Effects of Pudendal Nerve Stimulation are Frequency Dependent

- Inhibits bladder reflexes during low frequency stimulation (5-10 Hz).
- Facilitates bladder reflexes during higher frequency stimulation (20-30 Hz).
- Elicits urethral sphincter contractions to suppress voiding (5-30 Hz).
- Ultra high frequency stimulation (6-20 kHz) blocks axonal conduction, suppresses reflex sphincter contractions and promotes voiding.
Experimental Model to Study Pudendal Neuromodulation of the LUT

SCI 6 - 12 months

Sacral Cord

Pelvic Plexus

Infusion Pump

Pressure Recording

Bladder

External Urethral Sphincter

Pudendal N.

Electrical Stimulation at 0.5 – 40 Hz

(At low Hz inhibits reflex bladder contractions and at higher Hz induces reflex contractions)

Blocking electrode 5-10 KHz

(Suppresses Sphincter Dyssynergia)

(Tai, C., et.al., Neurourol Urodynam, 26:879, 2007)
Neuromodulation of the Spinal Micturition Switch by Pudendal Nerve Stimulation

High level afferent activity

Bladder

Elimination

OFF

Spinal Switch

Storage

ON

Urethral Sphincter

Pudendal Nerve Stimulation (6-10 Hz) promotes urine storage
Electrical stimulation of the perigenital region (EPGS) or pudendal nerve (EPNS) inhibits reflex bladder activity in a chronic SCI cat.

Multiple Effects of Pudendal Nerve Stimulation

Effect of electrical stimulation of the pudendal nerve (EPNS) on bladder capacity in spinal intact (normal) and chronic spinal injured cats (SCI). In SCI lower frequency stimulation (3-7 Hz) increases bladder capacity but higher frequency (20 Hz) has an excitatory effect and lowers bladder capacity.

Stimulation of Pudendal Nerve Afferents Elicits Inhibition by Two Mechanisms

• Activation of GABAergic inhibitory synapses in the lumbosacral spinal cord.

• Reflex activation of sympathetic nerve inhibitory reflexes to the bladder leading to release of norepinephrine and stimulation of β adrenergic inhibitory receptors.
Experiment for electrical stimulation and block of the pudendal nerve to promote voiding

Exciting (20-30 Hz)

Blocking (5-20 kHz)
Cystometry Showing Poor Voiding Efficiency after Chronic SCI

A. Spinal Intact

B. Chronic SCI

Tai, C., Neurourol Urodynamics, 26:879-886, 2007
Pudendal nerve stimulation (20Hz) induces a reflex bladder contraction after SCI but does not elicit voiding until motor axons to the urethral sphincter are blocked by ultra high frequency (10 kHz) stimulation.

Tai, C., Neurourol Urodynamics, 26:879-886, 2007
High level afferent activity evokes a bladder contraction.

Pudendal nerve stimulation (20-30 Hz) evokes a bladder contraction.

Bladder Contraction → Elimination ON

Storage ON

Spinal Switch

Urethral Sphincter Contraction

Poor Voiding

Pudendal Neuromodulation of the Spinal Circuit
Pudendal afferent stimulation (20-30 Hz) and block of motor axons (10 kHz) promotes voiding by evoking bladder contractions and blocking sphincter contractions.

- High level afferent activity

Bladder Contraction

- Voiding
- Urethral Sphincter Relaxation

Elimination

- ON

Spinal Switch

High Frequency Stimulation (10 kHz) induces axonal block

Pudendal nerve stimulation (20-30 Hz) evokes bladder reflex and promotes voiding
Combined Pudendal Afferent Stimulation (20 Hz) and Bilateral Motor Axon Block (10 kHz) Improves Urethral Flow at a Low Bladder Pressure after Chronic SCI.

Combined Pudendal Afferent Stimulation (20 Hz) with Unilateral or Bilateral Motor Axon Block (10 kHz) Improves Voiding Efficiency after Chronic SCI
Clinical Translation of Pudendal Neuromodulation to Improve Urinary Continence and Voiding after SCI.

- Dr. Changfeng Tai and the Department of Urology, University of Pittsburgh have a multi-year contract from the Department of Defense (DOD) to develop an implantable device to apply electrical stimulation at multiple sites on the pudendal nerve and at a range of frequencies to enhance bladder storage as well as voiding function after SCI.

- Methodology to be used in human studies is based on the results of Dr. Tai’s experimental studies in chronic spinal cord injured animals.

- The implanted device will be wireless controlled and externally rechargeable.
The implantable stimulator (A) and the locations of cuff electrodes implanted on the pudendal nerves in the cat (B). EUS – External Urethral Sphincter.
Types of Neuromodulation

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2. Sacral spinal root stimulation
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6. Epidural stimulation
Epidural Stimulation


Figure 1. The application target of the implantable spinal cord prosthesis on the rat and the electrode design schematic. Two types of the electrode array design (Upper: regular; lower: interlaced design) and two types of grid window on the electrodes are designed for future experiments.
Clinical and Experimental Animal Studies by Drs. Harkema, Hubscher and Edgerton

- In individuals with spinal injuries (AIS A-D, complete and incomplete) exercise training and epidural stimulation improves locomotor function. In addition bladder function and voluntary voiding also improves.
- Experiments in rats with complete spinal transection at the T8 segmental level revealed that chronic step training of 7 weeks duration in combination with 40 Hz epidural stimulation (L2-S1 spinal segments) enhances reflex voiding during routine cage activity as well as during treadmill stepping.
- Acute epidural stimulation in trained rats induces voiding at short latency.
- The studies suggest that spinal circuitry responsible for voiding can be upregulated by chronic physiological (exercise training) and electrically-induced neuromodulation.


Effects of exercise training on urinary tract function after spinal cord injury

Charles H. Hubscher, Lynnette R. Montgomery, Jason D. Fell, James E. Armstrong, Pradeepa Poudyal, April N. Herrity, and Susan J. Harkema

Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans

Claudia A. Angeli, V. Reggie Edgerton, Yury P. Gerasimenko and Susan J. Harkema
Conclusions

- Lower urinary tract dysfunction occurring after SCI is attributable to loss of supraspinal control and emergence of new spinal reflex mechanisms due to remodeling of spinal cord circuitry.

- New methods being developed in the field of bioelectronic medicine for electrical stimulation of spinal or peripheral axonal pathways may be useful as a supplement to pharmacotherapy and standard nursing care to normalize urine storage and voiding mechanisms in people with spinal cord injury.