Neural Control and Neuromodulation of Lower Urinary Tract Function

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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 TractFunctionsTwo Types of Voiding

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





Parkinson's, MS, stroke, brain tumors, spinal cord injury, aging, cystitis

Lower Urinary Tract Innervation





Two Types of Visceral Afferent Neurons: Bladder & Bowel



spinal cord

urinary bladder

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



The Bladder Urothelium



Afferent Nerve fiber

Urothelial-Afferent Interactions



Interaction of Sensory Pathways of Multiple Pelvic Organs

Convergent

Dichotomizing



Somatic and Visceral Afferent Convergence: Contribution to Visceral Referred Pain



Micturition Switching Circuit





Spinal Storage Reflexes

Supraspinal Voiding Reflexes



Voluntary Control of Voiding

Sensation of Bladder Filling



Prepared by C. J. Fowler

Voluntary Control of Voiding

Sensation of Bladder Filling



Inhibition of the Periaqueductal Gray (PAG) and Pontine Micturition Center (PMC) by the Forebrain Promotes Urine Storage



Urine Storage

Excitatory Signals from the Forebrain Elicits Voluntary Voiding







Coordinated Bladder Contraction and Urethral Sphincter Relaxation

Forebrain Circuitry Controlling Voiding



Pathophysiology of OA

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



References: 1. Fowler CJ.

Neuromodulation of the Micturition Switch



Sacral Neuromodulation

- 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



Sacral Spinal Nerve Root



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.



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)

The effects of spinal cord injury

•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



Supra-lumbar lesion

Bladder Sphingter Coordination: Effect of Spinal Cord Injury



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



Pudendal Neuromodulation of the LUT After Spinal Cord Injury in Cats



(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 5



Pudendal Nerve

PAG-PMC



Tibial Nerve

PAG-PMC



