



# Rehabilitation of Neurogenic Bladder Function

## Workshop 22

### Monday 23 August 2010, 14:00 – 18:00

Time	Time	Topic	Speaker
14:00	14.10	Welcome and Introduction	Karl-Dietrich Sievert
14.10	14.50	Peripheral and Central Mechanisms Contributing to Neurogenic Lower Urinary Tract Dysfunction.	William de Groat
14.50	15.30	Reinnervation of the Lower Urinary Tract after Cauda Equina Injury and Repair in Experimental Models	Leif Havton
15.30	16.00	Break	
16:00	16:40	Most recent advances in basic and clinical research – Afferent Nerve Simulation Affects the Spinal Circuits that Modulate Bladder and Sphincter Function	Ken Gustafson
16.40	17.20	Nerve Rerouting to Restore Voiding in Spina Bifida and SCI Rehabilitation of Neurogenic Bladder Function	Kenneth Peters
17.20	17:30	Conclusion, take home message	Karl-Dietrich Sievert

#### **Aims of workshop**

In the recent decades, the primary aim of urologists has been to treat neurogenic bladder dysfunction and improve lower urinary tract functionality through the use of antimuscarinics and self-catheterization. More recent treatment options such as botulinum toxin have been introduced and evaluated, however, they are not yet approved for urological indications. Sacral neurostimulation (e.g. Brindley stimulator) has been an option for some patients, however, the treatment requires additional deafferentiation. Other options have been evaluated but currently they are not necessarily considered a success. Nerve rerouting and even sacral neuromodulation (SNM) seem to have their indication in certain applications such as spinal cord injured (SCI) and nerve rerouting in spina bifida patients.

The most recent advances in basic and clinical research will be critically reviewed and discussed, including stem cell treatments, nerve rerouting and sacral nerve modulation. The aim of this course will be to report on the state of the art knowledge with respect to SCI and spina bifida pathology and pathophysiology while assessing the impact on the lower urinary tract functionality and to evaluate the prospective therapy options, which will be discussed with the audience.

#### **Educational Objectives**

This is a new workshop based on latest known technology to address the neurogenic bladder malfunction of SCI and spina bifida patients. To our knowledge, this data has not been previously presented together.

# Rehabilitation of Neurogenic Bladder Function

## 2010 ICS Workshop 22 Final outline

### **Aims and Objectives:**

The aim of this course will be to report on the state of the art knowledge with respect to SCI and spina bifida pathology and pathophysiology while assessing the impact on the lower urinary tract functionality and to evaluate the prospective therapy options, which will be discussed with the audience.

### **Educational Value:**

This is a new workshop based on latest known technology to address the neurogenic bladder malfunction of SCI and spina bifida patients. To our knowledge, this data has not been previously presented together.

### **Target Audience**

Advanced--Urologists, gynecologists, neuro-urologists, neurologists, pediatric urologists, researchers, clinicians involved in treating spinal cord or spina bifida patients

### **Keyword Description**

SCI, spina bifida, neurogenic bladder function

LUT rehabilitation (sacral neurostimulation/sacral neuromodulation, nerve re-routing)

### **Timing**

240 minutes

### **Description:**

In the recent decades, the primary aim of urologists has been to treat neurogenic bladder dysfunction and improve lower urinary tract functionality through the use of antimuscarinics and self-catheterization. More recent treatment options such as botulinum toxin have been introduced and evaluated, however, they are not yet approved for urological indications. Sacral neurostimulation (e.g. Brindley stimulator) has been an option for some patients, however, the treatment requires additional deafferentiation. Other options have been evaluated but currently they are not necessarily considered a success. Nerve rerouting and even sacral neuromodulation (SNM) seem to have their indication in certain applications such as spinal cord injured (SCI) and nerve rerouting in spina bifida patients.

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## Speaker: 1

- What is the current understanding of the normal innervation function of the lower urinary tract?
- Where do we stand in our knowledge from the information flow: urothelium; spinal nerve system; CNS, and back to the detrusor and the external sphincter and what are the control mechanisms?
- What are the current treatment options in the so-called idiopathic OAB?
- How successful are these approaches?

### **William de Groat, PhD, USA**

Dr. de Groat is a Distinguished Professor at the University of Pittsburgh's Pharmacology and Chemical Biology Department. He and his team are interested in the autonomic nervous system and the neural regulation of pelvic visceral functions. Current studies focus on the reflex control of the urogenital tract and the mechanisms underlying transmission at central and peripheral autonomic synapses. These experiments are designed to examine (1) the neurotransmitters in the reflex pathways, (2) neuroplasticity during postnatal development or following neural injury, (3) the neural pathways responsible for the detection of visceral pain, and (4) the actions of drugs used to treat urogenital dysfunction. His experiments have been conducted on a variety of preparations ranging from intact animals to isolated tissues, like spinal cord slices and dissociated neurons.

#### Recent research includes:

- Influence of naloxone on inhibitory pudendal-to-bladder reflex in cats. Chen ML, Shen B, Wang J, Liu H, Roppolo JR, de Groat WC, Tai C.
- Furuta A, K Asano, S Egawa, WC de Groat, MB Chancellor and N Yoshimura. Role of alpha 2-adrenoceptors and glutamate mechanisms in the external urethral sphincter continence reflex in rats. *Journal of Urology* 181:1467-1473, 2009
- Kullmann A, LA Birder, M Shah and WC de Groat. Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. *American Journal of Physiology: Renal Physiology* 296:F892-F901, 2009
- Fowler CJ, D Griffiths and WC de Groat. The neural control of micturition. *Nature Reviews Neuroscience* 9:453-466, 2008
- Kullmann F, D Artim, L Birder and WC de Groat. Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. *Journal of Neuroscience* 28:1977-1987, 2008

## Speaker: 2

- What is the difference between peripheral injury and SCI injury?
- Is there a pattern of mechanisms which are appearing during the “healing”?
- Is there a “best time of intervention” with regard to the injury itself?
- What are the state of the art approaches in research and when might we be able to have those in the clinic?

### Leif Havton, MD, PhD, USA

Leif A. Havton is a PhD and Assistant Professor in the Neurological Rehabilitation and Research Program at the David Geffen School of Medicine at UCLA. Dr. Havton has published papers and book chapters in the area of novel repair strategies to restore bladder function and peripheral nervous system regeneration.

Recent research includes:

- Chemotropic guidance facilitates axonal regeneration and synapse formation after spinal cord injury. Alto LT, Havton LA, Conner JM, Hollis li ER, Blesch A, Tuszynski MH. Nat Neurosci. 2009 Sep;12(9):1106-13..
- Chang HY, Havton LA. Re-established micturition reflexes show differential activation patterns after lumbosacral ventral root avulsion injury and repair in rats. Exp Neurol. 212(2):291-7 (2008).
- Chang HY, Havton LA. Differential effects of urethane and isoflurane on external urethral sphincter electromyography and cystometry in rats. Am J Physiol Renal Physiol. 295(4):F1248-53 (2008).
- Chang HY, Havton LA. Surgical implantation of avulsed lumbosacral ventral roots promotes restoration of bladder morphology in rats. Exp Neurol. 2008 Aug 9; (2008).
- Functional reinnervation of the rat lower urinary tract after cauda equina injury and repair. Hoang TX, Pikov V, Havton LA. J Neurosci. 2006 Aug 23;26(34):8672-9.

### Speaker: 1 and 2 Summary

- What is the difference between idiopathic and neurogenic lower urinary dysfunction?
- Why can't we approach them both in the same way?
- Where in the research do we find the evidence in nerve “bridging”?
- What might we expect form a rerouting (realistic vs. fiction: research translation)?

**BREAK**

## Speaker: 3

- What are neural prostheses, what are their differences and what are they able to do? How invasive are their placement? At which time after injury can we offer a patient a neural prosthesis and what is the expected success?
- Can afferent nerve stimulation restore bladder function or reduce sphincter spasms?
- Can nerve blocks eliminate sphincter activation and allow voiding?

### Ken Gustafson, Ph.D., USA

Dr. Gustafson is an Assistant Professor of Biomedical Engineering and Urology at Case Western Reserve University and a Research Scientist at the Cleveland VA Medical Center. His research interests focus on understanding the systems level neurophysiology and neural control of bladder and urethral functions and developing neural prostheses that interface with the nervous system to restore bladder function. Our research interests are focused in four parallel areas:

1. Basic neurophysiology studies to discover and characterize the neural pathways involved in bladder and urethral function.
2. Translational research projects to develop methods to conduct investigations in humans and lead to clinical implementation.
3. Clinical studies in individuals with and without neural dysfunction.
4. Neural engineering studies to design and develop neural prostheses appropriate for the "expected clinical applications."

Recent research includes:

- A Boger, N Bhadra, KJ Gustafson. Bladder Voiding by Combined High Frequency Electrical Pudendal Nerve Block and Sacral Root Stimulation. *Neurourol Urodyn*, 27(5): 435-439, 2008.
- Mariano TY, Bhadra N, Gustafson KJ. Suppression of reflex urethral responses by afferent stimulation in an acute spinalized feline model. *Neurourol Urodyn* 29(3):494-500, 2010.
- Bruns TM, Bhadra N, Gustafson KJ. Bursting stimulation of proximal urethral afferents improves bladder voiding. *J Neural Engineering*. 9;6(6):66006, 2009.
- Bruns TM, Bhadra N, **Gustafson KJ**. Variable patterned pudendal nerve stimuli improves reflex bladder activation, *IEEE Trans Neural Syus Rehabil Eng*, 16(2): 140-148,2008.

## Speaker: 4

- In which context can we currently place the clinical expectation nerve modulation and nerve stimulation?
- If injuries in the spinal cord are supposed to be bridged, how much function can be expected?
- Are there different indications and what results from that success rates?
- Do we have an evaluated evidence-based outcome?

### **Kenneth Peters, MD, USA**

Dr. Peters is the chairman of the Department of Urology at Beaumont Hospital in Royal Oak since 2007. Dr. Peters is widely known for his work on nerve rerouting surgery, interstitial cystitis and neuromodulation. He has written numerous peer-reviewed journal articles and book chapters on incontinence, interstitial cystitis and neuromodulation and has twice won the SUFU clinical research award.

Recent research includes:

- Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmIT trial. Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, Macdiarmid SA. *J Urol.* 2010 Apr;183(4):1438-43.
- Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. MacDiarmid SA, Peters KM, Shobeiri SA, Wooldridge LS, Rovner ES, Leong FC, Siegel SW, Tate SB, Feagins BA. *J Urol.* 2010 Jan;183(1):234-40.
- Chronic pudendal neuromodulation: Expanding available treatment options for refractory urologic symptoms. Peters KM, Killinger KA, Boguslawski BM, Boura JA. *Neurourol Urodyn.* 2009 Sep 28.
- A prospective, single-blind randomized crossover trial of sacral vs. pudendal nerve stimulation for interstitial cystitis, Peters KM, Feber KM, Bennett RC. *BJU Int.* 2007 Oct;100(4):835-9.
- The relationship between subjective and objective assessments of sacral neuromodulation effectiveness in patients with urgency-frequency. Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, Macdiarmid SA. *J Urol.* 2010 Apr;183(4):1438-43.

## Chairman, Speaker 5, Conclusion and Take Home Message

- Single center results of nerve-rerouting after SCI
- New clinical approaches in neuro modulation/stimulation?

### **Karl-Dietrich Sievert, MD, PhD, Germany**

Professor Sievert is the Vice Chair and Director of the Uro-oncology, Neuro-urology, Incontinence and Reconstructive Urology at the University of Tuebingen (Germany) where he founded an interfunctional network/collaboration for the Continence Center and Spinal Cord Unit. Professor Sievert's long interest in rehabilitation of neurogenic bladder function extends back to his doctoral dissertation was "Selective Sacral Root Stimulation by using sinusoidal signal and specific organ frequency for the physiological bladder evacuation".

Recent research includes:

- Early sacral neuromodulation prevents urinary incontinence after complete spinal cord injury *Annals of Neurology* Early View K.-D Sievert, B. Amend, G. Gakis, P. Toomey, A. Badke, H.P. Kaps, A. Stenzl
- Latest technologic and surgical developments in using InterStim Therapy for sacral neuromodulation: impact on treatment success and safety. Spinelli M, Sievert KD. *Eur Urol.* 2008 Dec;54(6):1287-96. Epub 2008 Feb 8.
- Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. Amend B, Hennenlotter J, Schäfer T, Horstmann M, Stenzl A, Sievert KD. *Eur Urol.* 2008 May;53(5):1021-8. Epub 2008 Jan 17. PMID:
- Subcutaneous tunneling of the temporary testing electrode significantly improves the success rate of subchronic sacral nerve modulation (SNM). Sievert KD, Nagele U, Pannek J, Engeler D, Kuczyk M, Stenzl A. *World J Urol.* 2007 Dec;25(6):607-12.
- Voluntary micturition after intradural nerve anastomosis Sievert KD, Xiao CG, Hennenlotter J, Seibold J, Merseburger AS, Kaminskie J, Nagele U, Stenzl A. *Urologe A.* 2005 Jul;44(7):756-61. Review. German.

## Speaker 1

### **Peripheral and Central Mechanisms Contributing to Neurogenic Lower Urinary Tract Dysfunction ICS 2010-Toronto Canada**

William de Groat  
Distinguished Professor  
Pharmacology and Chemical Biology Department  
University of Pittsburgh Medical School  
Pittsburgh, PA

#### **Introduction**

Spinal cord injury (SCI) rostral to the lumbosacral level eliminates voluntary and supraspinal control of voiding leading initially to an areflexic bladder and complete urinary retention, followed by a slow development of automatic micturition and neurogenic detrusor overactivity (NDO) mediated by spinal reflex pathways {1,2}. However voiding is commonly inefficient due to simultaneous contractions of the bladder and urethral sphincter (detrusor-sphincter-dyssynergia, DSD). Electrophysiologic studies in SCI animals revealed that NDO depends on the reorganization of synaptic connections in the sacral spinal cord and the emergence of a spinal micturition reflex pathway activated by capsaicin sensitive C-fiber bladder afferent nerves {1,3}. Sufficient clinical evidence exists to support the view that a comparable process occurs in man following a spinal lesion resulting in extensive efforts to therapeutically reduce the C-fiber afferent input using intravesical or intramural administration of neurotoxins (capsaicin, resiniferatoxin or botulinum toxin).

#### **Plasticity in Bladder Afferent Pathways**

Changes in the morphological, electrical and chemical properties of C-fiber bladder afferent neurons including alterations in ion channels and transmitter expression contribute to NDO. Studies in patients with NDO resulting from multiple sclerosis or various types of spinal cord injury have revealed increased TRPV1, P2X<sub>3</sub> and pan-neuronal marker (PGP9.5) staining in suburothelial nerves and increased TRPV1 staining in the basal layer of the urothelium {1-3}. Treatment of NDO patients with intravesical capsaicin or resiniferatoxin, reduces the density of these immunoreactive nerves and urothelial TRPV1 immunoreactivity in the subpopulation of these patients exhibiting symptomatic improvement. Injections into the bladder wall of botulinum neurotoxin type A (BoNT/A), an agent that blocks the release of neurotransmitters from urothelial cells and from afferent and efferent nerves also reduces NDO and reduces the density of TRPV1- and P2X<sub>3</sub>-immunoreactive nerves but does not alter TRPV1- and P2X<sub>3</sub>-staining in



the urothelium. These results suggest that an abnormality of the C-fiber afferent innervation contributes to NDO.

Electrophysiological studies in animals provide further support for plasticity in the afferent limb of the micturition reflex after SCI {3}. In spinal intact cats micturition is mediated by the pontine micturition center and is triggered by myelinated ( $A\delta$ ) bladder afferents; whereas in SCI cats the spinal micturition reflex is triggered by unmyelinated (C-fiber) afferents (Fig. 1) that are normally unresponsive to distension of the bladder (thus termed "silent C-fibers"). Systemic administration of capsaicin which desensitizes C-fiber afferent nerves blocks reflex micturition in SCI cats but does not alter reflex micturition triggered by  $A\delta$  afferents in spinal cord intact animals. These data indicate that changes in the central connections and the electrical properties of C-fiber bladder afferent neurons are responsible for the emergence of automatic micturition after SCI. Chemical interactions between the urothelium and adjacent C-fiber bladder afferent nerves may contribute to NDO. The urothelium has neuron-like properties that allow it to respond to physiological and noxious stimuli and in turn release a number of signaling molecules including ATP, acetylcholine, NGF, nitric oxide and neurokinins {4-6}. These molecules can act on receptors on afferent nerves to modulate their excitability. Administration of a  $P2X_3$  purinergic receptor antagonist to chronic SCI rats reduces pre-micturition contractions during bladder filling and increases bladder capacity suggesting that endogenously released ATP facilitates bladder reflex activity after SCI presumably by increasing the excitability of afferent nerves {7}.

Chronic spinal injury in humans also causes the emergence of an unusual bladder reflex that is elicited by infusion of cold water into the bladder (the Bors Ice Water Test). The response to cold water does not occur in normal adults but does occur in: (1) infants, (2) in patients with suprasacral cord lesions, (3) patients with multiple sclerosis and Parkinson's disease, and (4) elderly patients with hyperactive bladders. Studies in animals indicate that cold temperature activates TRPM8 and possibly other temperature sensitive receptors in bladder C-fiber afferents (Fig. 1) and/or urothelial cells. Intravesical administration of capsaicin to spinal cord injured patients blocks the cold-induced bladder reflexes, indicating that they are mediated by C-fiber afferents. The presence of the cold reflex in infants, its disappearance with maturation of the nervous system, and its re-emergence under conditions in which higher brain functions are disrupted suggests that it represents a primitive spinal involuntary voiding reflex. Patch clamp recordings in bladder afferent neurons in rats and cats indicate that SCI increases the excitability of the C-fiber neurons by reducing A-type  $K^+$  currents and by switching high threshold  $Na^+$  currents to low threshold more easily activated  $Na^+$  currents thereby lowering the threshold for generating firing {3}. This change in electrical properties must contribute to awakening of silent C-fiber afferents. In the cat where vasoactive intestinal polypeptide (VIP) is expressed in bladder C-fiber afferent axons the VIP-containing afferent projections in the spinal cord expand and reorganize after SCI. These observations raise the possibility that C-fiber bladder afferents sprout and contribute to the synaptic remodeling in the spinal micturition

reflex pathway that occurs after SCI. The pharmacological effect of VIP, on bladder activity is also changed after SCI. Intrathecal administration of VIP which suppresses reflex bladder activity in cats with an intact spinal cord, enhances or unmasks reflex bladder activity in chronic SCI cats.

Changes in morphology, neuropeptide expression and function of C-fiber afferents have also been detected in the rat after SCI. The changes include: (1) hypertrophy of bladder afferent neurons in the L<sub>6</sub>-S<sub>1</sub> DRG, (2) increase in expression of PACAP-IR in bladder DRG neurons and expansion of PACAP-IR afferent axons in the lumbosacral spinal cord. PACAP is a close relative of VIP, (3) expansion of CGRP and IB4 containing primary afferent fibers in the spinal cord prior to the recovery of reflex bladder activity, (4) association of CGRP and IB4 staining with GAP-43 staining in afferent fibers in SCI rats indicating that afferents were sprouting.

### **Role of Nerve Growth Factor in Plasticity of Bladder Reflexes after SCI**

Neurotrophic factors including nerve growth factor (NGF) have been implicated as chemical mediators of pathology-induced changes in C-fiber afferent nerve excitability and reflex bladder activity. After SCI in rats the levels of NGF increase in the bladder, in the lumbosacral spinal cord and in the DRG. In the bladder NGF may originate from multiple sources including smooth muscle and urothelial cells. The stimulus for increased levels of NGF appears to be overdistension of the bladder due to DSD.

Intravesical administration of NGF in rats acutely increases reflex bladder activity and chronic administration of NGF into the spinal cord or into the bladder wall of rats induces bladder hyperactivity and increases the firing frequency of dissociated bladder afferent neurons. NGF might act by multiple mechanisms because it is known that it upregulates PACAP and TRPV1 expression in DRG neurons and downregulates A-type K<sup>+</sup> channel currents. Endogenous NGF seems to contribute to the lower urinary tract dysfunction after SCI because intrathecal application of NGF antibodies, which neutralize NGF in the spinal cord, suppresses detrusor hyperreflexia and detrusor-sphincter-dyssynergia (DSD) in SCI rats. This treatment with NGF antibodies produces effects similar to the effect of desensitizing C-fiber afferents with capsaicin or resiniferatoxin.

In humans with NDO or idiopathic detrusor overactivity (IDO), increased levels of NGF have been detected in bladder tissue and in the urine. After injections of botulinum toxin (BoNT/A) into the bladder wall, patients that exhibited reduced symptoms also had reduced urinary NGF levels. Thus, it has been proposed that NGF may be a sensitive biomarker for the diagnosis NDO and IDO and may be a useful tool for evaluating the therapeutic effect of BoNT/A injections. NGF and its receptors in the bladder and/or the spinal cord may be important targets for new therapies to reduce voiding dysfunction after SCI.

## **Reorganization of Synaptic Connections in the Spinal Cord after SCI**

Spinal cord injury in cats and rats not only causes the emergence of automatic micturition but also causes the re-emergence of a neonatal exteroceptive micturition reflex that is activated by tactile stimulation of cutaneous afferent axons in the perineum (i.e., the perineal-to-bladder reflex). In neonatal animals, this reflex is activated by the mother licking the perineal region of the young animal. The adult form of reflex voiding, that is triggered by bladder distension, does not become functional until several weeks after birth. As the adult reflex is appearing, the neonatal perineal-to-bladder reflex becomes progressively weaker and eventually disappears. Thus, postnatal maturation of voiding function is associated with a prominent reorganization of synaptic connections in bladder reflex pathways, leading to down-regulation of primitive spinal mechanisms and up-regulation of mature supraspinal mechanisms. This developmental switching mechanism seems to be dependent upon competition between brain and spinal pathways because spinal cord injury in adult animals and humans, which interrupts brain-spinal cord connections, causes the re-emergence of the neonatal perineal-to-bladder reflex as well as the neonatal cold-evoked bladder reflex. Patch clamp recordings in neonatal rat spinal slice preparations indicate that interneuronal glutamatergic excitatory synaptic inputs to bladder preganglionic neurons are prominent in young animals but downregulated during postnatal development as excitatory bulbospinal inputs mature {8}. Spinal cord injury that eliminates the bulbospinal pathways causes the upregulation of the spinal interneuronal connections. This pattern of synaptic reorganization presumably underlies the recovery of bladder reflexes after spinal cord injury in humans.

## **Conclusions**

Neurogenic detrusor overactivity (NDO) is attributable to a reorganization of spinal reflex mechanisms as well as a change in the properties of peripheral afferent nerves. A greater understanding of the pathophysiological mechanisms underlying NDO should facilitate the development of new treatments for neurogenic lower urinary tract dysfunctions.

## **References:**

1. Fowler, C.J., Griffiths, D., and de Groat, W.C. The neural control of micturition. *Nature Reviews Neuroscience*, 9: 453-466, 2008.
2. Birder, L., de Groat, W.C., Mills, I., Morrison, J., Thor, K. and Drake, M. Neural control of the lower urinary tract: peripheral and spinal mechanisms. *Neurourology and Urodynamics*, 29: 128-139, 2010.
3. de Groat, W.C. and Yoshimura, N. Changes in Afferent Activity After Spinal Cord Injury. *Neurourology and Urodynamics*, 29: 63-76, 2010.
4. Birder, L.A., de Groat, W.C. and Apodaca, G. Physiology of the Urothelium, IN: *Textbook of the Neurogenic Bladder*, second edition. Chapter 3. Eds. Shick, E. and Corcos, J., Taylor and Francis, London, UK, 19-39, 2008.

5. Kullmann F., Artim D., Birder L., de Groat W.C. Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. *Journal of Neuroscience*, 28: 1977-1987, 2008
6. Kullmann F., Artim D., Beckel J., Barrick S., de Groat W.C., Birder L. Heterogeneity of muscarinic receptor mediated  $Ca^{2+}$  responses in cultured urothelial cells from rat. *Am J Physiol Renal Physiol*, 294: F971-F981, 2008.
7. Lu SH, Groat WC, Lin AT, Chen KK, Chang LS. Evaluation of purinergic mechanism for the treatment of voiding dysfunction: a study in conscious spinal cord-injured rats. *Journal of the Chinese Medical Association*, 70: 439-444, 2007.
8. Araki, I. and de Groat, W.C. Developmental synaptic depression underlying reorganization of visceral reflex pathways in the spinal cord. *Journal of Neuroscience*, 17: 8402-8407, 1997.

**Figure 1**

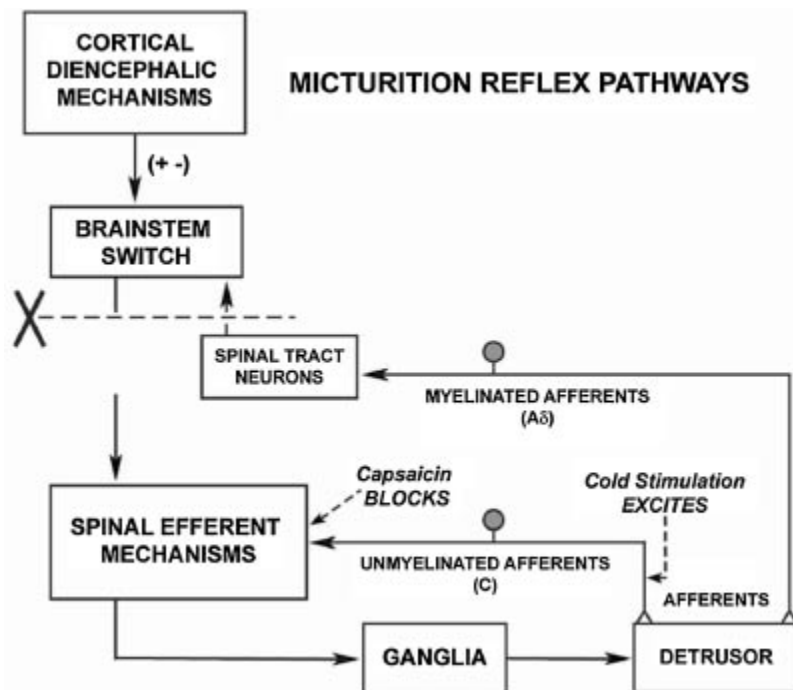


Diagram showing the organization of the parasympathetic excitatory reflex pathway to the detrusor muscle. Scheme is based on electrophysiologic studies in cats. In animals with an intact spinal cord, micturition is initiated by a supraspinal reflex pathway passing through a center in the brain stem. The pathway is triggered by myelinated afferents (A $\delta$ -fibers), which are connected to the tension receptors in the bladder wall. Injury to the spinal cord above the sacral segments (X) interrupts the connections between the brain and spinal autonomic centers and initially blocks micturition. However, over a period of several weeks following spinal cord injury, a spinal reflex mechanism emerges, which is triggered by unmyelinated vesical afferents (C-fibers); the A-fiber afferent inputs are ineffective. The C-fiber reflex pathway is usually weak or undetectable in animals with an intact nervous system. Stimulation of the C-fiber bladder afferents by instillation of ice water into the bladder (cold stimulation) activates voiding responses in patients with spinal cord injury. Capsaicin (20–30 mg, subcutaneously) blocks the C-fiber reflex in chronic spinal cord injured cats, but does not block micturition reflexes in intact cats. Intravesical capsaicin also suppresses detrusor hyperreflexia and cold evoked reflexes in patients with neurogenic bladder dysfunction.

## Speaker 2

### Reinnervation of the Lower Urinary Tract after Cauda Equina Injury and Repair in Experimental Models ICS 2010-Toronto Canada

Leif Havton  
PhD and Assistant Professor  
Neurological Rehabilitation and Research  
David Geffen School of Medicine  
University of California  
Los Angeles, CA

#### Overall Goals of Presentation:

To provide participants with:

- 1) A thorough understanding of fundamental differences between a spinal cord injury and injuries to the peripheral nervous system, including the lumbosacral nerve roots (cauda equina).
- 2) An understanding of patterns of mechanisms, which appear during spontaneous “healing” after injuries to the sacral spinal cord (conus medullaris) and cauda equina.
- 3) An understanding of biological, medical, and surgical issues, which influence decisions on “best time of intervention.”
- 4) An understanding of current state-of-the-art approaches in research on conus medullaris/cauda equina injury and repair, opportunities and challenges for clinical translation, and when new treatments may be introduced in the clinic.

#### What is the difference between peripheral and spinal cord injuries?

Injuries to the peripheral nervous system denervate peripheral target organs and result in a **lower motoneuron syndrome**. In contrast, an injury to the spinal cord interrupts ascending and descending projections in the spinal cord and results in an **upper motoneuron syndrome**. The lower urinary tract function may be impaired by both lower and upper motoneuron lesions:

Effects of an anatomically complete conus medullaris lesion and/or cauda equina injury (**lower motoneuron injury**):

- 1) Loss of voluntary micturition
- 2) Atonic/hypotonic bladder
- 3) Impaired external urethral sphincter muscle

Effects of injuries between the pontine micturition center in the brain stem and the sacral portion of the spinal cord (**upper motoneuron injury**):

- 1) Hyper-reflexic bladder
- 2) Detrusor-sphincter dyssynergia
- 3) Poorly sustained bladder contractions
- 4) Increased post-micturition residual volume

Note that injuries to the spinal cord typically result in a lower motoneuron syndrome at the segmental level of injury and an upper motoneuron syndrome below the level of lesion. For combined traumatic injuries to the sacral portion of the spinal cord and cauda equina, the clinical presentation of paralysis, sensory dysfunction, and autonomic impairments is referred to as a **conus medullaris syndrome** (Maynard et al., 1997). Interestingly, a prior survey has indicated that recovery of autonomic/pelvic organ functions is ranked as one of the highest priorities by the spinal cord injured population (Anderson, 2004). However, there are no effective treatments available to repair lost neurological function in patients with conus medullaris/cauda equina injury.

### **Is there a pattern of mechanisms which appear during the “healing” phase?**

Intramedullary lesions to the conus medullaris and proximal lesions to the ventral roots of the cauda equina (avulsion injuries) result in a series molecular, cellular, and neural systems changes, which take place over days and weeks, and contribute to the resultant clinical phenotype. These changes include:

- 1) Retrograde degeneration and death of axotomized autonomic and motor neurons mediated by apoptosis and necrosis
- 2) Reactive astrocytic gliosis in the spinal cord gray and white matters
- 3) Inflammatory responses in spinal cord white and gray matters involving both microglia and macrophages
- 4) Sensory plasticity with functional reorganization of spinal cord reflexes and emergence of acute-to-chronic neuropathic pain

### **Is there a best time of intervention with regard to the injury itself?**

Present surgical approach: Following admission to the acute hospital, many patients with traumatic injuries to the conus medullaris/cauda equina may within hours or days undergo surgical decompression of the spinal cord with the removal of, for instance, free bone fragments, foreign bodies, and blood clots. The spine may also be stabilized. However, no procedures are available for reversing lost neurological function.

Future treatment opportunities: Because the lesioned lumbo-sacral spinal cord and cauda equina are accessible during spinal cord decompression and spine stabilization surgeries in post-traumatic patients, new treatments involving a surgical component may be introduced as add-on procedures during the acute to sub-acute time window.

A best time window for treatment interventions is likely but may vary depending on the nature of each intervention. The following aspects need to be taken into consideration when designing new treatment interventions for patients with conus medullaris/cauda equina injuries:

- 1) Retrograde loss of axotomized autonomic and motor neurons takes place over days and weeks. This potential limitation is important for any pharmacological and surgical neuroprotective strategies.
- 2) Surviving axotomized autonomic and motor neurons express regeneration associated genes, which may promote axonal regeneration, over days to weeks
- 3) Denervated Schwann cells in nerve roots and peripheral nerves may show a decline in their ability to support the growth of regenerating axons over time. This is especially a limitation for the re-innervation of distal peripheral targets.
- 4) A glial scar and inflammatory reactions follow traumatic lesions to the conus medullaris and cauda equina. These effects may change the host environment for cell transplantation/replacement strategies in subjects with chronic injuries.

## **What are the current state of the art approaches in research and the potential for new treatments?**

Lumbosacral ventral root avulsion injuries in animal models provide an opportunity to study the effects of a “worst case scenario” for cauda equina injuries. A ventral root avulsion injury results in separation of the ventral roots from the ventral root exit zone and represent an injury to the central nervous system. Ventral root avulsion injuries require axonal regeneration within the spinal cord for repair and functional recovery to be accomplished.

In rat models, an acute surgical re-implantation of avulsed lumbosacral ventral roots has demonstrated several effects, which are of translational research interest. Specifically, re-implantation of avulsed ventral roots promotes:

- 1) Neuroprotection of axotomized autonomic and motor neurons (Hoang et al., 2006a)
- 2) Axonal regeneration by spinal cord neurons into re-implanted ventral roots (Hoang et al., 2006a)
- 3) Reinnervation of the lower urinary tract with re-establishment of reflex micturition (Hoang et al., 2006b; Chang and Havton, 2008a)
- 4) Restoration of bladder morphology (Chang and Havton, 2008b)
- 5) Amelioration of neuropathic pain (Bigbee et al., 2008)

Surgical repair using re-implantation of avulsed ventral roots have previously been demonstrated to reinnervate skeletal muscle and provide functional improvement in both experimental models and humans with brachial plexus injuries (Carlstedt et al., 1995, 2000; Cullheim et al., 1989; Havton and Carlstedt, 2009)



### Features/Advantages:

- 1) Root re-implantation procedures can be added to existing spine surgery for spinal cord decompression and spine stabilization Axonal regeneration by spinal cord neurons into re-implanted ventral roots (Hoang et al., 2006a)
- 2) Relatively quick introduction to clinical trials is possible, as treatment is a surgical procedure using patient's own tissues; therefore, no FDA approval is required.

### Challenges:

- 1) The surgical anatomy of the human conus medullaris/cauda equina needs to be better defined and training provided to participating surgeons.
- 2) Injuries to extended portions of avulsed/transected ventral roots will be present in some/many subjects with conus medullaris/cauda equina injuries; a nerve graft would be needed to bridge tissue gap between the lumbosacral spinal cord and lesioned ventral roots in such cases.

### Possible graft materials to bridge between spinal cord and lesioned ventral roots

- 1) Nerve graft tissues obtained from the patient:
  - A) Sensory nerve segment (e.g. sural nerve)
  - B) Intercostal nerve segment (mixed nerve)
  - C) Lesioned dorsal roots: As severed dorsal roots are presently considered "impossible" to repair, lesioned dorsal root segments may serve as nerve grafts with the advantage of being used without inflicting additional neurological deficits to the subject
- 2) Biomaterials (artificial nerve grafts/nerve guidance tubes) – need to be compatible for use in humans and approved by the FDA; if successful, would not require inflicting any new lesion for harvesting nerve grafts.

Although surgical replantation of avulsed/severed ventral roots appears promising as a new possible treatment option for acute conus medullaris/cauda equina injuries, there is still room for improvement. Combinatorial treatment strategies may be considered to augment treatment effects. Presently, several different strategies are being investigated in research laboratories and include:

- 1) Pharmacological approaches to increase neuroprotection and axonal regeneration using drugs that are already approved by the FDA for other purposes (for instance minocycline, riluzole) (Bergerot et al., 2004; Hoang et al, 2008). FDA-approved drugs may be able to enter clinical trial testing expeditiously after demonstration of convincing effect in experimental models.
- 2) Gene therapy approaches to deliver e.g. neurotrophic factors to increase neuronal survival and axonal regeneration after ventral root avulsion injury and root re-implantation (Eggers et al., 2008). Gene therapy approaches are associated with more regulatory controls before consideration for clinical trial testing and are therefore likely to take longer to reach the clinic compared to e.g. FDA-approved pharmacological agents.

Chronic injuries to the conus medullaris/cauda equina represent a different treatment challenge. However, it is an important and large patient group. In patients with chronic injuries, surgical re-implantation of avulsed/transected ventral roots into the lumbosacral spinal cord is not likely to be sufficient for meaningful recovery to take place, as a marked neuronal loss has been completed. Therefore, cell replacement treatment strategies may also be considered and are currently being investigated in research laboratories. Several different types of cells are being considered for transplantation purposes and include the following sources:

- 1) Human embryonic stem cells
- 2) Adult neural stem cells
- 3) Human induced pluripotent stem cells (iPS)

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## Speaker 3

### **Most Recent Advances in Basic and Clinical Research Afferent Nerve Stimulation Affects the Spinal Circuits that Modulate Bladder and Sphincter Function ICS 2010-Toronto Canada**

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#### **Functional Electrical Stimulation**

Functional Electrical Stimulation (FES) is the application of electrical stimulation to restore function. FES can be applied for therapeutic purposes or for replacement of lost function.

The Cleveland FES Center develops technology that improves the quality of life of individuals with disabilities through the use of FES and enables the transfer of the technology into clinical deployment.

Neural Prostheses are devices that connect directly with the nervous system and use FES to replace or supplement function.

#### **Neural prostheses to restore bladder function “Bladder Pacemakers”**

Sacral root stimulation (Brindley approach) can eliminate bladder hyper-reflexia and provide on-demand voiding. However this approach requires an irreversible dorsal rhizotomy that eliminates any remaining sensation and bowel and sexual reflexes, which prevents many individuals from accepting this technology.

A number of neural prosthetic approaches are in development that can potentially restore function without a rhizotomy.

#### **Afferent stimulation of sacral neural circuits**

Spinal circuits control bladder and urethral activity. Afferent (sensory) nerve stimulation can affect (positively or negatively) these spinal circuits and modulate activity. This approach takes advantage of the native neural circuitry and is potentially less invasive than sacral root stimulation. Stimulation effects are strongly dependent on the pattern of stimulation.

#### Bladder inhibition and activation

- Afferent stimulation of pudendal nerve fibers can both reduce bladder reflexive contractions to provide continence and provide bladder excitation.
- Sacral root neuromodulation and peripheral nerve stimulation can inhibit bladder activity.

#### Urethral sphincter inhibition and activation

- Pudendal nerve stimulation can provide efferent (motor) closure of the urethral sphincter
- Recent animal work suggests that afferent nerve stimulation can reduce aberrant urethral reflexes and allow bladder voiding

### **Electrical nerve block of the urethral sphincter for bladder voiding**

High frequency alternating currents can temporarily block nerve conduction. This approach provides immediate, complete and reversible nerve block or “electrical lidocaine”.

Pudendal nerve block can eliminate urethral sphincter activation. Pudendal block combined with sacral root stimulation for bladder activation produces bladder voiding equivalent to complete pudendal nerve transaction.

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## Speaker 4

### Nerve Rerouting to Restore Voiding in Spina Bifida and SCI Rehabilitation of Neurogenic Bladder Function ICS 2010-Toronto Canada

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- Spina bifida is a congenital defect affecting approximately 0.2/1000 live births in the United States
- SCI occurs in about 15-40 cases/million with about 11,000 new cases occurring yearly in the US
- The inability to urinate normally is a consequence of both conditions (neurogenic voiding dysfunction) and is a major health problem.
- Traditional *electrical* neuromodulation is not effective in treating the voiding dysfunction associated with spina bifida and complete spinal cord injury
  - In spina bifida the nerves do not fully develop and innervate the urinary system below the lesion making electrical modulation ineffective
  - In spinal cord injury, the nerves to the bladder are intact, but no afferent signal can get to the central nervous system due to the cord lesion making electrical neuromodulation ineffective.
- Xiao introduced the concept of an artificial voiding reflex by the intradural microanastomosis of a healthy lumbar motor root to a sacral motor recipient root.
- The procedure is performed at the intradural root level, so that the dorsal root (sensory) is left intact.
- Xiao proved this concept in animals and demonstrated that the somatic nerve could reinnervate the bladder
- To stimulate a bladder contraction the appropriate cutaneous dermatome is scratched, sending a signal down the dorsal root, to the cord and ultimately down the ventral root to the bladder and sphincter resulting in a coordinated contraction.
- In humans, the development of the new reflex may require up to 18 months of

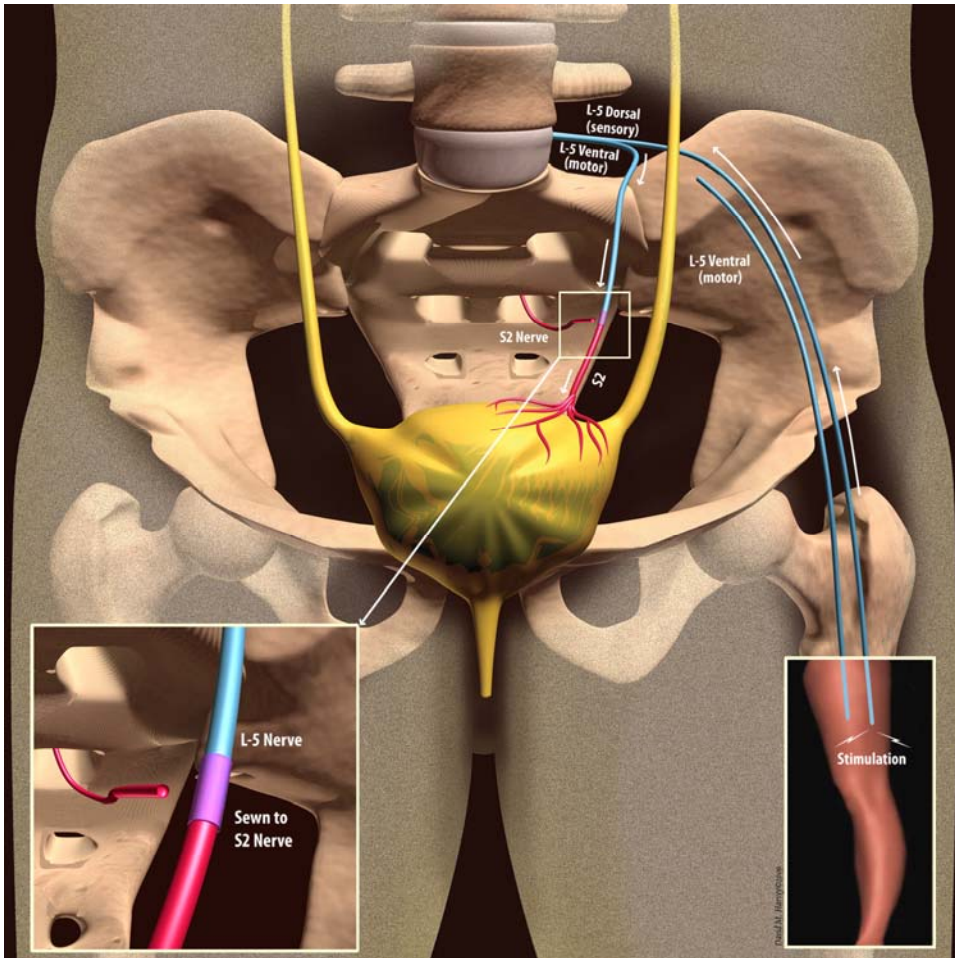
regenerative time.

- Xiao<sup>7</sup> reported his experience with 92 SCI patients and 110 spina bifida patients in 2005, reporting an 87% success rate at one year.
- The most profound and unexpected finding was the development of bladder and bowel sensory function in the spina bifida children who gained storage and emptying function and the ability to initiate micturition without the need to stimulate the sensory dermatome.
- All of the human data reported in the literature in spina bifida was performed in China
- There is a need to duplicate this data in the United States
- We have reported our experience on 9 patients who underwent lumbar to sacral nerve rerouting to restore voiding and improve bowels
- Seven of nine subjects developed a cutaneous to bladder reflex suggesting the rerouting can occur in humans
- It is imperative that we gather robust clinical data to determine the risk benefit profile. If this technique is proven to work, then we can focus on making this a better procedure and identifying ways to improve outcomes and reduce adverse events.
- A difficult aspect of this study is to how to define success given there is a constellation of symptoms associated with neurogenic bladder and bowel
- Importantly, does the benefit of the procedure outweigh the inherent risks, particularly to the lower extremity?
- Is success defined as demonstrating a detrusor contraction with stimulation of the dermatome? If this is the definition of success than this surgery clearly works for the majority of patients.
- In addition, a number of patients have noted a change in their voiding and bowel function with several reporting improvements including increased sensation of the bowel and bladder, new ability to initiate voiding, improved bowel function, less detrusor overactivity and the ability to stop antimuscarinics. Is this enough to define success?
- Clinical trials on Lumbar to Sacral nerve rerouting are ongoing in the United States

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**FIGURE 1**





## **Speaker 5**

### **Conclusion/Take Home Message ICS 2010-Toronto Canada**

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