Pelvic Neuromodulation

Daniel Rapoport

Urology Grand Rounds

March 14, 2007

D.O. Circa 1982, Sherwood Park AB

" ability to void or inhibit voiding…sets humans apart from all other mammals"

Lapides

Pelvic Neuromodulation

- **Definition**
- Neurophysiology
- Mechanism
- Clinical aspects

Definition

- Not in stedman's

Definition

- "therapeutic alteration of activity in the central, peripheral or autonomic nervous systems, electrically or pharmacologically, by means of implanted devices "

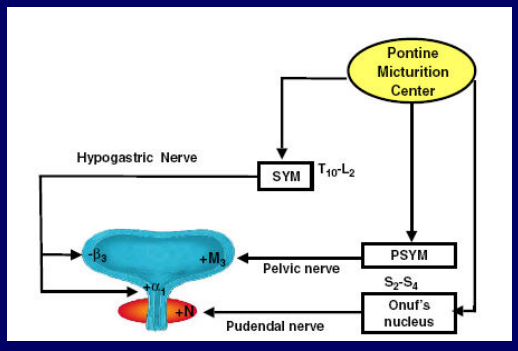
North American Neuromodulation Society

- "stimulating nerves to improve bodily functions and patient symptoms"

Resnick. Urol Clinic NA 2005

Spectrum

- Nerve stimulation
  - Cerebral
  - Spinal cord
  - Peripheral
  - Percutaneous
  - Endoscopic
- Drug Delivery
  - Intrathecal
  - Peripheral (botox)



Applications

- CNS
  - Pain syndromes
  - Spasticity
  - Epilepsy
  - Movement disorders
- ENT
  - Cochlear implants
- Cardiac
  - Pacemaker
  - ICD

Treatment of chronic ventilatory failure using a diaphragmatic pacemaker

H Garrido-Garcia[1,*], J Mazaira Alvarez[1], P Martín Escribano[2], J Romero Ganuza[1], F La Banda[1], C Gambarrutta[1], ME Garcia L[1], C Labarta[1], O Arroyo[1], F Sebastián de la Cruz[1], R Gutierrez[1] and J García Moreno[1]

[1]National Hospital for Paraplegics, Toledo, Spain; [2]Pneumology Department, Hospital 12 de Octubre, Madrid, Spain

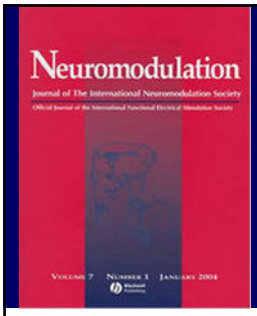
Neuromodulation in Urology

- Nerve stimulation at various targets of neuraxis
  - Transurethral Bladder Stimulation
  - Direct Detrusor Stimulation
  - Spinal Cord Stimulation
  - **Sacral Root Stimulation**
  - Peripheral/cutaneous Nerve Stimulation
  - Pharmaconeuromodulation

Figura 2.
Dispositivo De InerStim® Sacral Neuromodulation

Organizations

- Societies
  - International Neuromodulation Society
  - North American Neuromodulation Society
- SUFU
  - International Society of Pelvic Neuromodulation
- Fellowships
  - Several FPMRS programs include neuromodulation training



Highlights From the Combined Society of Urodynamics and Female Urology, and International Society of Pelvic Neuromodulation Annual Meeting

Gary E. Lemack,*,† Cindy Amundsen,‡ Gopal Badlani,§ Tomas Griebling,‖ Kenneth Peters,¶ Larissa Rodriguez, Ajay Singla,** Christopher Smith,†† Maryrose Sullivan and Alexis Te‡‡

1st Annual Meeting of the Canadian Neuromodulation Society

Canadian Neuromodulation Society

Pelvic Neuromodulation

- Definition
- **Clinical aspects**
- Neurophysiology
- Mechanism

The Niche

- Target Population?
  - Idiopathic voiding dysfunction
  - Chronic pelvic pain
  - Off label: DES, SUI, ED, NGB (SCI/MS)
- What does it offer?
  - Option for those failing conservative mgmt
  - Avoid irreversible surgical mgmt

Neuromodulation Indications

- FDA approved:
  - Storage disorders (urge incontinence, OAB)
  - Voiding disorders (non-obstructive retention)
- Expanding uses:
  - Chronic Pelvic Pain syndromes
  - Neurogenic bladder dysfunction
  - Stress urinary incontinence
  - Pediatric voiding dysfunction
  - Erectile dysfunction
  - Fecal incontinence/Constipation

Clinical Evaluation of Voiding Dysfunction

- History
  - Detail LUTS
  - Triggering events: diet, surgery, trauma, radiation
  - Detailed list of conservative therapies
- Questionnaires + Voiding diary
  - Objectify symptoms
  - ICIQ, OAB-q

Cambpell's 9th ed.

Siegel. Urol Clin NA; 32(1) 2005

Clinical Evaluation of Voiding Dysfunction

- Physical Examination
  - "Hurts to sit", pelvic floor spasm
  - SUI, hypermobility, prolapse
  - Neurologic exam
  - Pelvic floor examination

Cambpell's 9th ed.

Siegel. Urol Clin NA; 32(1) 2005

Clinical Evaluation of Voiding Dysfunction

- Urinalysis
  - Cytology in selected cases
- Urodynamics
  - CMG, EMG, PFS
  - Indications: previous surgery, mixed LUTS, suspect NGB, failed medical mgmt
- Cystoscopy
- Imaging
  - Ultrasound
  - MRI spine in selected cases

Cambpell's 9th ed.

Siegel. Urol Clin NA; 32(1) 2005

Defining the Disorder: OAB

- Terminology
  - Symptoms of frequency and urgency +/- incontinence, in absence of pathology
- Clinical Definition (varies)
  - 4 episodes of urgency in previous 4 wk
  - > 8 voids/day
- Epidemiology
  - 17% (9% wet) of women; 16% (2.5% wet) of men
- Natural History
  - Lack of long-term follow up data

Garnett. J Urol; 169(4) 2003

Defining the Disorder: Idiopathic Retention

- A.K.A. Fowler Syndrome
  - Female < 30 yrs
  - Unable to void > 24 hrs
  - No urge + PVR > 1 litre
  - NO neurologic findings, MRI (-), cysto (-)
  - UDS
    - Acontractile detrusor
    - Inappropriate EUS contraction
    - Inability to relax EUS

Campbell's 9th Ed

Defining the Disorder: Idiopathic Retention

- In Males with idiopathic retention… consider:
  - Bladder neck dysfunction
    - Diagnosis by VUDS
    - Treated with A-blockers or “channel TURP”
  - Bashful Bladder
    - Low-pressure/low-flow voiding
    - Difficult to demonstrate objectively
    - Difficult to treat

Patient Selection

- Indications
  - OAB (wet or dry)
  - Idiopathic retention
- Failed conservative management
  - Behavioral; Dietary; Pelvic Floor exercises; Biofeedback; Pharmacotherapy
  - **Peripheral nerve stimulation**
  - Botox

Siegel. Urol Clin NA; 32(1) 2005

Predictors of Success

- Good response on trial phase is only predictor
- No clinical factors predict success of neuromodulation

Contraindications

- Absolute
  - Anatomic abnormality of sacrum or sacral nerves
  - Mental incapacity
  - Failed trial stimulation
- Relative
  - Neurologic lesion (unstable)
  - MRI studies
  - Other stimulation devices

Cambpell's 9th ed.

Siegel. Urol Clin NA; 32(1) 2005

How It's Done

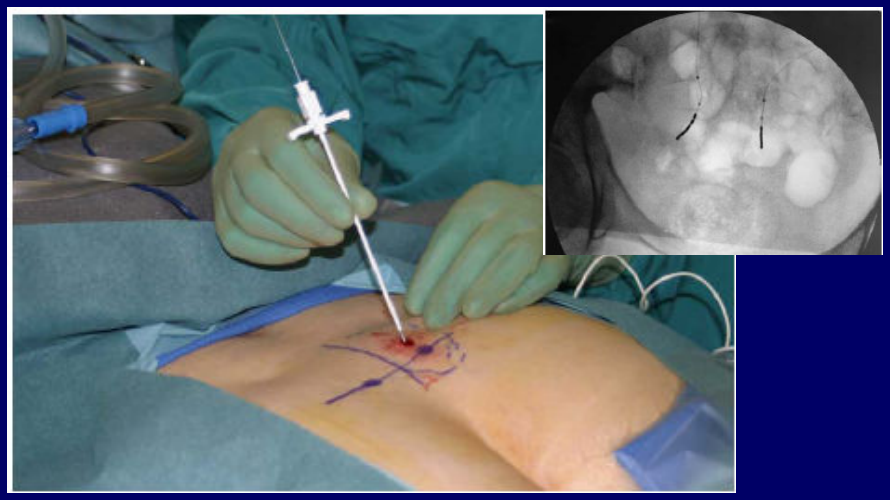
- 2 step process
  - Testing (stage 1)
  - Implantation (stage 2)
- Both can be done under combined sedation + local anesthesia

Chai. Urol Clin NA; 32(1) 2005

Test Phase

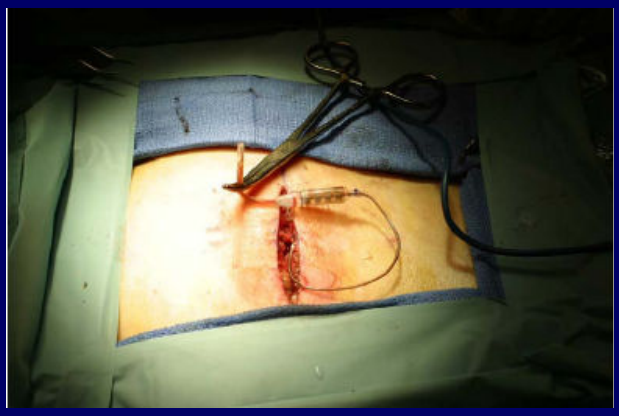
- Percutaneous implantation at S3 foramina
  - Fluoroscopic guidance
  - S3 reflexes: anal wink, great toe dorsiflexion
- Tined lead
  - Prevents migration (false negative)
- 1 - 4 week trial
  - Voiding diary,
  - > 50% improvement

Chai. Urol Clin NA; 32(1) 2005



Implantation

- Subcutaneous pouch
- Upper buttock, lower abdomen
- One implantable pulse generator per lead
  - 2 IPGs if bilateral



Efficacy

- Only 4 RCTs
  - 3 by SNS Study Group
- Several case series
- Lack of long term data

SNS STUDY GROUP
Schmidt et al. J Urol; 162(2) 1999

- Prospective multicenter (16) RCT
- Evaluate SNS for refractory urge incontinence

Inclusion Criteria	Exclusion Criteria
• Age greater than 16 years • Refractory to standard medical therapy • 100 Ml. bladder capacity with normal upper urinary tract • Good surgical candidate • Able to complete study documentation and return for followup evaluation	• Neurological conditions (multiple sclerosis, diabetes with peripheral nerve involvement, spinal cord injury, stroke) • Stress urinary incontinence • Primary pelvic pain

Method

- 155 patients underwent test stimulation
- 76 patients with > 50% improvement randomized to implantation or delay

TABLE 1. *Demographic summary of 155 patients with urge incontinence*

No. women (%)	125 (80.6)
No. men (%)	30 (19.4)
Mean age ± SD (range)	46.6 ± 13.0 (20.2–78.9)
Mean yrs. urinary symptoms ± SD before enrollment (range)	9.0 ± 7.4 (0.6–35.4)
No. previous medical treatment for urinary problems (%).*	153 (98.7)
Pharmacological	144 (92.5)
Nonsurgical	55 (35.5)
Surgical	88 (56.8)

* Medical treatment categories were not mutually exclusive.

Efficacy Measurement

- Clinical (Voiding Diary)
  - Evaluated @ 1, 3, 6 mo and then q6 mo
  - Control group allowed to crossover 6 mo
  - Deactivated stimulation after 6 mo
- QOL
  - SF-36 Health Survey
- Urodynamic parameters
  - Baseline vs 6 mo
  - Treatment vs control, treatment pre & post

Voiding Diary Effect

TABLE 3. *Sustained clinical benefit 18 months after implant*

	% 6 Mos. After Implant (58 pts.)	% 12 Mos. After Implant (38 pts.)	% 18 Mos. After Implant (21 pts.)
Any leaking episode:			
Dry	47	45	52
50% Reduction or greater	28	34	24
Total clinical success	75	79	76
Heavy leaking episodes:			
Eliminated	77	70	84
50% Reduction or greater	13	10	0
Total clinical success	90	80	84
Absorbent pads or diapers replaced daily:			
Eliminated	57	55	57
50% Reduction or greater	26	21	19
Total clinical success	83	76	76

Schmidt et al. J Urol; 162(2) 1999

Deactivation after 6 months

- N = 52
- 3-7 day deactivation

	SNM ON	SNM Off	
Leaks/day	2.9	9.5	<.001
Severity	.8	2	<.001
Pads/day	1.2	5.8	<.001

Schmidt et al. J Urol; 162(2) 1999

QOL Effect

- Significant improvement in perceptions of physical health status
- No treatment patients got worse

Urodynamic Effect

- No significant changes
- No de novo retention
- No de novo detrusor overactivity

SNS STUDY GROUP Urgency-Frequency

- 29 patients, 2 yr f/u
- Voiding Diary
  - 56-64% significant (>50%) improvement in
    - Voids per day
    - Voided volumes
    - Urgency score
- QOL
  - Statistically significant improvements in several domains of SF-36

Hassouna et al. J Urol; 163(6) 2000

SNS STUDY GROUP
Idiopathic Retention

- 42 patients, 2 yr f/u
  - 5.6 cath/day, 343 mL/cath
- Voiding Diary
  - 70% significant (>50%) reduction in cath volumes
  - 58% eliminated cath usage altogether

Jonas et al. J Urol; 165(1) 2001

Durability

- Prospective case series (OAB)
- 45 patients, mean f/u 47 months
- 60% significant improvement
  - 20% cured
- Reasons for failure
  - Recurrent lead migration/breakage
  - Explantation for infection
- All failures occurred w/in 18 mo

Bosch. J Urol; 163(4) 2000

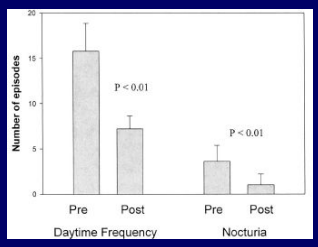
Expanding Indications: IC

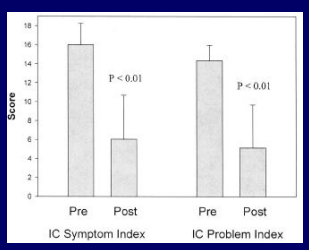
- 25 patients
  - NIDDK criteria IC
  - Failed behavioral, drugs and hydrodistention after 6 months
- Underwent test stimulation
  - 7 days, Voiding diary
- Data measured
  - Daytime frequency, nocturia
  - Voided volume
  - IC symptom and problem index scores

Comiter. J Urol; 169(4) 2003

Comiter. J Urol; 169(4) 2003

- 17 patients had > 50% improvement
  - implantated
- Mean 14 mo f/u
  - Improved freq/noct
  - Improved pain scores
  - Improved voided volumes
  - Improved ICSI/ICPI





Safety

Table 1
Reported complication with sacral neuromodulation therapy from the neuromodulation study group

Complication	Probability of occurrence (Siegel series)
Pain at neurostimulator site	15.3%
New pain	9.0%
Suspected lead migration	8.4%
Infection	6.1%
Transient electric shock	5.5%
Pain at lead site	5.4%
Adverse change in bowel function	3.0%
Technical problems	1.7%
Suspected device problems	1.6%
Change in menstrual cycle	1.0%
Adverse change in voiding function	0.6%
Persistent skin irritation	0.5%
Suspected nerve injury	0.5%
Device rejection	0.5%
Others	9.5%

Seigel. Urol; 2000

Complications of SNS

- Test Stimulation (18% complication rate)
  - Lead migration
  - Technical problems
  - Pain
- Post-implantation (15% complication rate)
  - Pain at IPG site
  - Infection
- 33% re-operation rate
  - Revision and explantation

Seigel. Urol; 2000

Cleveland Clinic Case Series

- 167 patients, 2 yr follow-up
- Indications
  - OAB, IUR
  - IC
  - Neurogenic retention

Vasavada. Urol Clin NA; 32(1) 2005

CCF: Stage 1 Complications

- 72% went on to implantation
  - 2-4 wk test stimulation
  - Percutaneous tined lead
- Of the 28% test leads removed
  - 92% poor clinical response
  - 8% infection
- 12% required revision
  - Marginal response
  - Migration/lead problem

CCF: Stage 2 Complications

- 12% Explant
  - 56% infection
  - 43% to maintain response
- 20% Revisions
  - Infections, mechanical reasons

Generator Site Infection

- Best management is explantation
- Salvage often not successful
  - Ie. Relocation
- Pain at generator site, no infection
  - Generator relocation

Management of Response Decrease

- Impedance testing
  - Open circuit
    - High impedence, no current flow
  - Short circuit
    - Low impedence, high current flow (to wrong area)
    - Body fluid/tissue intrusion into wires
    - Current follows path of least resistance

Management of Response Decrease

- Response-related revision are most common case of stage 2 revisions

Future

- Special Populations
  - Pediatrics
  - Neurogenics
- Expanding Indications
  - ED
- Technical advances/improvements

LONG-TERM RESULTS OF SACRAL NERVE STIMULATION (S3) FOR THE TREATMENT OF NEUROGENIC REFRACTORY URGE INCONTINENCE RELATED TO DETRUSOR HYPERREFLEXIA

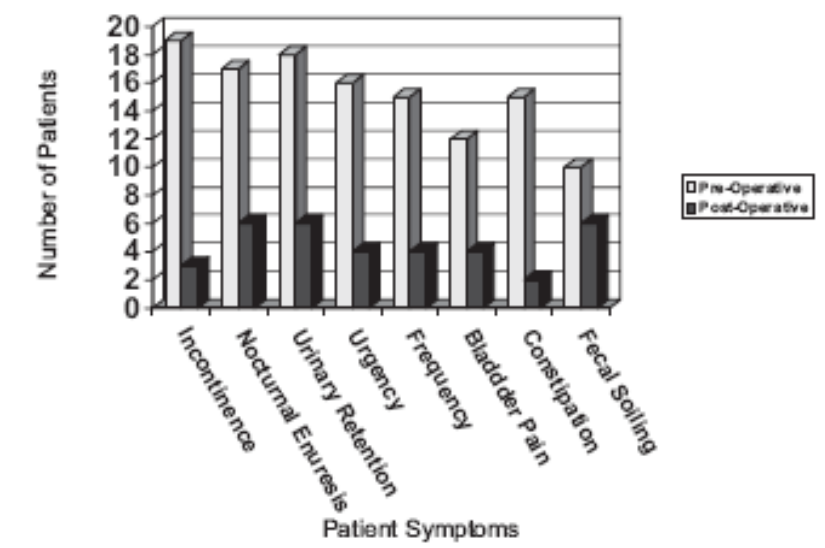
EMMANUEL J. CHARTIER-KASTLER, J. L. H. RUUD BOSCH, MICHEL PERRIGOT, MICHAEL B. CHANCELLOR,* FRANÇOIS RICHARD† AND PIERRE DENYS

- 9 women with NGB and incontinence
  - 2 MS, 2 myelitis, 5 SCI
  - All had neurogenic DO
  - refractory to antichol.
  - 5 with DESD
- 40 mo f/u
  - Improved urodynamic and clinical parameters in most
  - Increased DO in 1 patient

Preliminary Results of Sacral Neuromodulation in 23 Children

Mitchell R. Humphreys, David R. Vandersteen, Jeffery M. Slezak, Pam Hollatz, Craig A. Smith, Janet E. Smith and Yuri E. Reinberg*

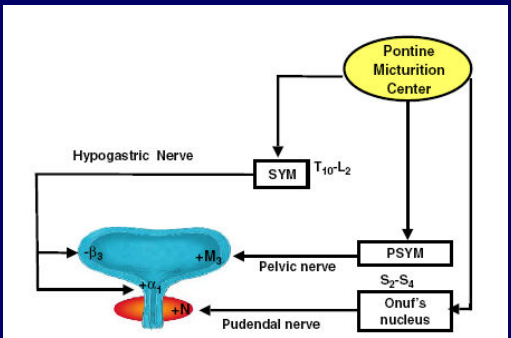
- 23 children age 6-15
- Severe DES
  - Negative work-up (US,VCU, UDS, MRI)
  - Failed 6 mo conservative/medical mgmt
  - "highly motivated' families
- 21/23 responded to test stimulation



- Definition
- Clinical aspects
- **Neurophysiology**
- Mechanism

Overview

- **Neuroanatomy**
  - **Peripheral**
  - **Central**
- Neurophysiology
  - reflexes

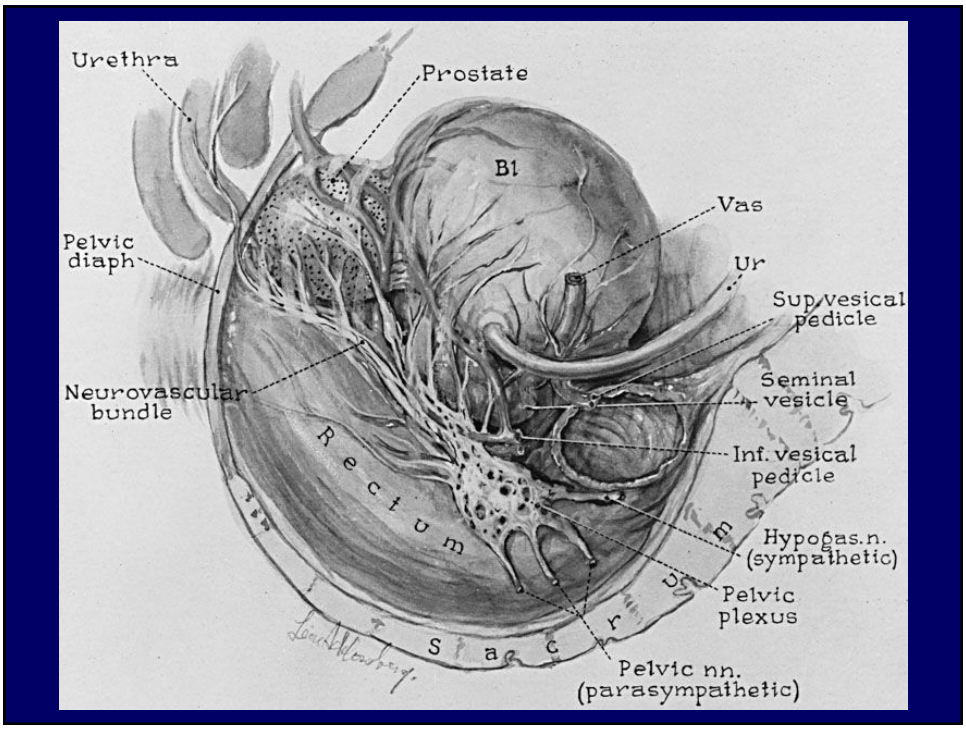


Peripheral Efferent Pathways

1. Sacral parasympathetics
   - excite bladder, inhibit outlet
2. Thoracolumbar sympathetics
   - inhibit bladder, excite outlet
3. Pudendal nerves
   - excite external sphincter

Peripheral Efferent Pathways

	Structures	Function
Parasympathetic	**S 2,3,4** Ganglia in detrusor wall **Pelvic plexus** **(Perirectal)**	**Voiding**
Sympathetic	**T 10 – L2** Sympathetic chain ganglia Inferior mesenteric ganglia **Hypogastric nerves** **Pelvic Plexus**	**Storage**
Somatic	**S 2,3,4** Onuf's nucleus **Pudendal nerve**	S: genitalia, pelvic viscera M: EUS contraction



Peripheral Afferent Pathways

1. Somatic: pudendal nerves
   - sensory info from genitals, pelvic viscera
2. Autonomic: pelvic and hypogastric nerves
   - A-delta fibres:
     - Located in smooth muscle
     - Sense bladder fullness
   - **C-fibres:**
     - **Located in mucosa and smooth muscle**
     - **Sense noxious stimuli**

De Groat. Urol Clin NA; 23(2), 1996

Leng. Urol Clin NA; 32(1) 2005

C-Fibres

- Most are silent
- Recruitment with inflammation/pathology
- Become mechanosensitive, low threshold
- Implicated in detrusor overactivity
- Therapeutic target
  - Capcaisin
  - RTX
  - **Neuromodulation**

Leng. Urol Clin NA; 32(1) 2005

Central Pathways

	Structures	Function
Cortex	Frontal ACG	Sensation, social context Control - "on-off" spinal reflexes - external sphincter
Brainstem	PMC	Coordinates bladder and sphincter - Reflex and voluntary
Spinal Cord	Afferent pathways - dorsal Efferent Pathways - ventral Interneurons	Interface between brain and periphery Interface b/w peripheral afferents & efferents

Efferents to LUT activated by

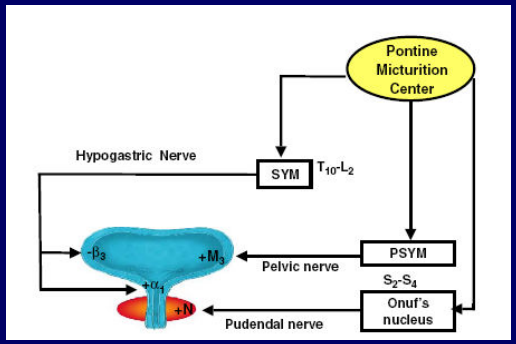
- Signal from peripheral afferents
  - Eg. Reflex voiding in infants
- Signal from brain
  - Eg. Volitional voiding

- Unique organ:

  " Visceral organ under mostly voluntary control"

Overview

- Neuroanatomy
  - Peripheral
  - Central
- **Neurophysiology**
  - **reflexes**



Storage Reflex

- Passive (“default mode”)
- Reflex arc contained within spinal cord
- Low bladder wall tension → low-intensity afferent signal results in:
  - Sympathetic outflow to bladder & outlet
  - Somatic outflow to external sphincter
  - Inhibition of parasympathetic outflow

De Groat. Urol Clin NA; 23(2), 1996

Storage Reflex

- External sphincter contraction (somatic)
- Internal sphincter contraction (sympathetic)
- Detrusor inhibition (sympathetic)
- Parasympathetic inhibition (sympathetic)

De Groat. Urol Clin NA; 23(2), 1996

Emptying Reflex

- Voluntary or reflex initiation
- Mediated by PMC (Spino-bulbar-Spinal)
- High bladder wall tension → high-intensity afferent signal results in:
  - Parasympathetic outflow to bladder & outlet
  - Somatic outflow to sphincter
  - Inhibition of sympathetic outflow

De Groat. Urol Clin NA; 23(2), 1996

Emptying Reflex

- Inhibit external sphincter (somatic)
- Inhibit internal sphincter (parasymp.)
- Detrusor contraction (parasymp.)
- Inhibit sympathetic outflow (parasymp.)

De Groat. Urol Clin NA; 23(2) 1996

Interneurons

- Interneurons in spinal cord allow for communication b/w sympathetic, parasympathetic and somatic pathways
  - GABA, glycine, enkephalin mediated

Van Balken. J Urol; 172(2), 2004

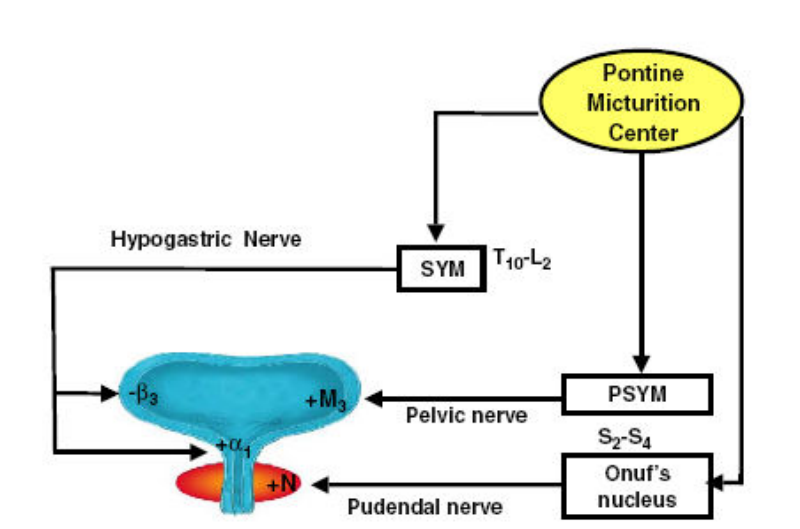
De Groat. Urol Clin NA; 23(2) 1996

Reflexes and Neuromodulation

- Reciprocal autonomic reflex arcs
  - Sympathetic (storage) vs Parasympathetic (emptying)
  - "off balance"
    - Afferent over/underactivity
    - Efferent over/underactivity
    - Central signalling dysfunction
- Autonomic, Somatic & Central pathways converge in spinal cord
  - Activation of one effects the other
  - Gate-control theory

- Definition
- Clinical aspects
- Neurophysiology
- **Mechanism**

Neuromodulation Mechanism



Neuromodulation Mechanism: What is "known"

- Efferent outflow to the LUT is activated by
  - Periphery: autonomic afferents (reflex) or
  - Central: supraspinal efferents
- Somatic spinal afferents (pudendal nerves) can modulate voiding function
  - Eg. Vincent's Curtsy, Kegel's

De Groat. Urol Clin NA; 23(2), 1996

Neuromodulation Mechanism: What is "Known"

- Primary action: triggers **somatic afferents**
  - Stimulus under threshold for autonomics/motor
  - Common pathway to affecting micturition and storage reflexes

Leng. Urol Clin NA; 32(1) 2005

Van der Pal. Curr Opin Urol;16(1) 2006

Neuromodulation Mechanism: What is "Known"

- Somatic afferent stimulation secondary effects:
  - Autonomic efferents
    - Directly
    - Indirectly (through afferent limb of reflex arc)
  - Autonomic afferents
    - Directly
    - Through interneurons
  - Supraspinal centres
    - Direct
    - Indirect
    - Chronic changes (neuroplasticity)

Leng. Urol Clin NA; 32(1) 2005

Neuromodulation Mechanism What is "Proposed"

- Induces physiologic changes in sphincter muscle and pelvic floor
- Induces chronic changes (neuroplasticity) in higher centers
- Enhances nerve regeneration stimulation of neurotrophin secretion

Storage Disorders (OAB)

- Proposed pathophysiology:
  - Increased afferent firing and reflex voiding
    - C-fibre recruitment
    - establishment of new low threshold pathways
  - Altered CNS inhibition of reflex voiding

Storage Disorders (OAB)

- Proposed therapeutic mechanism:
  - Inhibit afferent firing
    - Inhibit parasympathetic efferent
  - Re-establish central inhibition

Storage Disorders (OAB): Peripheral Effect

- Inhibit bladder afferents **
- Inhibit parasympathetic efferents
  - Indirect reflex inhibition
  - Indirect activation sympathetic efferents
- Direct stimulation of Onuf's nucleus (not supported)
  - No direct sphincter contraction

Van der Pal. Curr Opin Urol;16(1) 2006
Leng. Urol Clin NA; 32(1), 2005

Storage Disorders (OAB): Central Effect

- Activates central inhibitory areas
  - Functional MRI evidence
    - activation of somatosensory and somatomotor cortex
- ? Chronic brain changes (neuroplasticity)

Van der Pal. Curr Opin Urol;16(1) 2006
Leng. Urol Clin NA; 32(1) 2005

Idiopathic Retention

- Proposed pathophysiology:
  - Brain unable to turn off guarding reflex
    - Bladder-sympathetic reflex
  - Pelvic floor spasm leads to reflex inhibition of detrusor
  - Essentially DSD without SCI

Van der Pal. Curr Opin Urol;16(1) 2006
Leng. Urol Clin NA; 32(1) 2005

Idiopathic Retention

- Proposed therapeutic mechanism:
  - Inhibit afferent limb of guarding reflex
    - Indirectly inhibit sympathetic outflow to bladder/urethra
  - Stabilize pelvic floor
  - Activate PMC

Idiopathic Retention: Peripheral and Central Effect

- Inhibit afferent limb of guarding reflex**
  - Reflex inhibition of sympathetic efferents to bladder and outlet
- Elimination of pelvic floor/sphincter spasticity
- Activation of PMC
  - Conflicting data from PET studies

Van der Pal. Curr Opin Urol;16(1) 2006
Urol Clin NA, 32(1) 2005

Chronic Pelvic Pain / IC

- Gate-control theory (Melzack and Wall, 1965)
  - Activity in low threshold afferents inhibits firing of nociceptive afferents through an inhibitory interneuron
  - Activity in pudendal afferents/A-delta afferents inhibit firing of c-fibres through interneurons in substantia gelatinosa

Alo. Neurosurgery; 50(2), 2002
Van der Pal. Curr Opin Urol;16(1) 2006