Bladder motility during filling: mechanisms, function and dysfunction

W12B, 29 August 2011 16:00 - 17:30

Start	End	Topic	Speakers
16:00	16:25	The generation and modulation of motor/sensory noise: physiology, pharmacology and pathology	• James Gillespie
16:25	16:30	Questions	All
16:30	16:55	The origins and roles of non-voiding bladder contractions	• Matthew Fraser
16:55	17:00	Questions	All
17:00	17:25	Clinical relevance of non-micturition bladder contractility	• Marcus Drake
17:25	17:30	Questions	All

Aims of course/workshop

Autonomous bladder motility not associated with micturition has been documented since the late 1800s. This workshop will review the mechanisms and functions of non-voiding bladder contractile activity in both health and disease. The non-neural cellular networks responsible for coordinated motility and localized micromotions, as well as the influences of the autonomic nervous system on these networks, will be described. Clinical correlates and translation of animal data will be discussed in terms of normal physiology and pathophysiological conditions.

Educational Objectives

That the bladder shares with other visceral smooth muscle autonomous motility has been known since the late 1800s. However, efforts to make use of this knowledge and apply it toward understanding the normal physiology and pathophysiology of the lower urinary tract have been relatively few in number. Those that have pursued the elucidation of the mechanisms involved in non-voiding bladder motility have made great strides in understanding both the interactions of non-neuronal cell types with other non-neuronal cell types and the interactions of non-neuronal cells with the autonomic nervous system. Moreover, the insights gleaned from this line of research may ultimately explain the origins of urgency and detrusor overactivity, thereby allowing us to better design approaches to treat these contributors of overactive bladder. This workshop will educate the delegates in the latest discoveries and interpretations pertaining to non-micturition bladder motility, with emphasis on clinical correlates and preclinical translation.

The generation and modulation of motor/sensory noise: physiology, pharmacology and pathology

Professor JI Gillespie

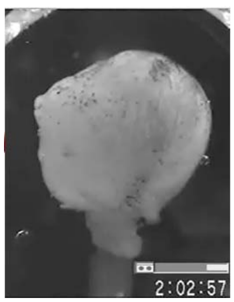
The Department of Psychiatry and Neuropsychology
Maastricht University
Maastricht
The Netherlands

The Dental and Medical School
Newcastle University
Newcastle upon Tyne
England

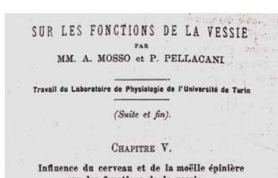
Maastricht University

Newcastle University

The surprising bladder



Motor activity generated in the bladder

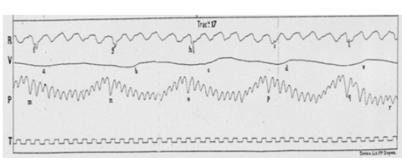

SUR LES FONCTIONS DE LA VESSIE
PAR
MM. A. MOSSO et P. PELLACANI

Travail du Laboratoire de Physiologie de l'Université de Turin

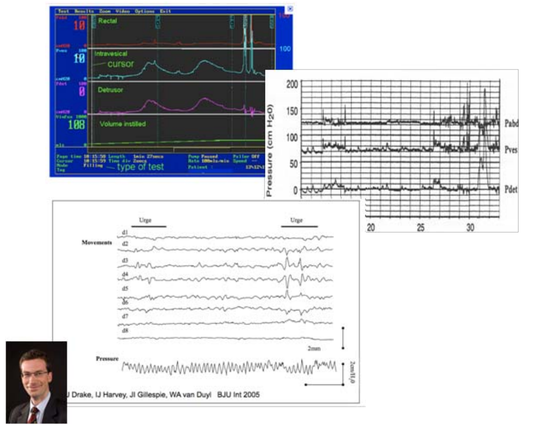
(Suite et fin).

CHAPITRE V.

Influence du cerveau et de la moëlle épinière sur les fonctions de la vessie.



Mosso and Pellacani Arc Ital Biol 1882: 1: 291



Motor Activity in the Bladder – Autonomous Activity

Sherrington CS. Notes on the arrangement of some motor fibres in the (lumbo-sacral plexus**. J Physiol 1892: 13: 621-772**

CS Sherrington (1852-1927)

In order to determine the action of nerves on a quiescent bladder ……..'I endeavoured first to bring the bladder into a condition of rest free from rhythmic contraction by performing a transverse section of the spinal cord'… 'I was surprised to find that (this) did not arrest the movements of the bladder'……..

Non-voiding contractions
Non-voiding activity (NVA)

'Similar contractions……..can be obtained by removing the viscus from the recently killed animal, placing it in normal saline solution at 38°C….For this purpose the bladder of the dog answers better than the Macacus…..

Contractile events generated within the bladder wall – Autonomous Activity

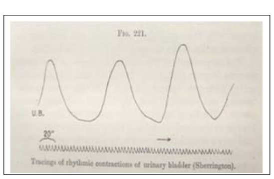
'We must now enquire into the mechanisms of the act of expulsion. As the urine slowly trickles into the bladder this viscus first relaxes to accommodate the fluid, so that its contents increase without corresponding rise in intra-vesical pressure………'

'With increasing distension however the pressure in the bladder begins to rise, and this increased tension on the muscle walls has the ordinary excitatory effect on the muscle fiber ………'

'Slow rhythmic contractions of the bladder make their appearance and increase in force with increasing tension on the muscle walls (Fig. 221)………'

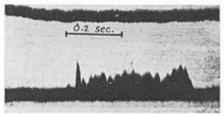
'These rhythmic contractions, causing a waxing and waning of intra-vesical pressure, start impulses up the afferent nerve fibers of the bladder to the lumbo-sacral cord, and here a continual summation of these impulses goes on, until finally, as the bladder is contracting, the stored-up impulses break through all resistance and give rise to reflex discharge down efferent motor nerves of the bladder………..'

Elements of Human Physiology
Starling 1905

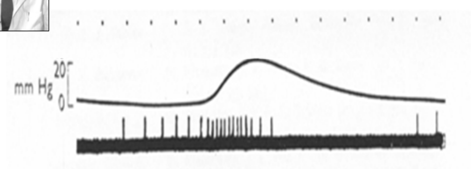


Motor/Sensory System

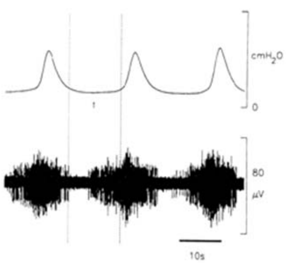
Phasic discharge in bladder afferents



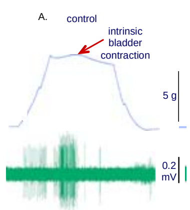
Talaat M 1940, J Physiol 89; 1-13



Iggo A. J Physiol 1955: 128: 593-607



Vaughan CW, Satchell PM. J Neurophysiol 1992: 68: 1842-1849



A Kanai 2011

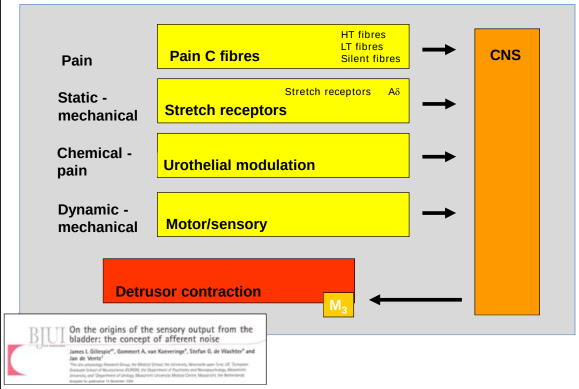
Afferent information
Sensory information

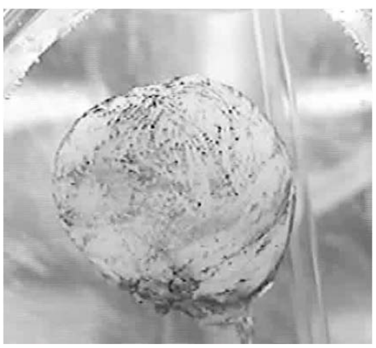
'The impulses from visceral fibres on the central nervous system appear hardly at all to elicit conscious sensation. When abnormally they do so, it is as though particular afferents, which usually in the strict meaning of the term sensory fibres at all, can on occasion become sensory'

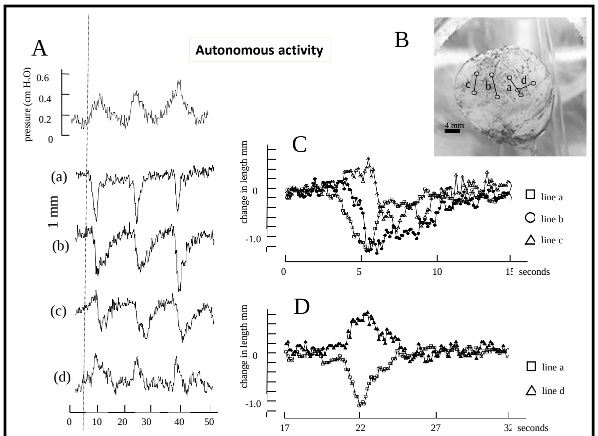
CS Sherrington (1900).

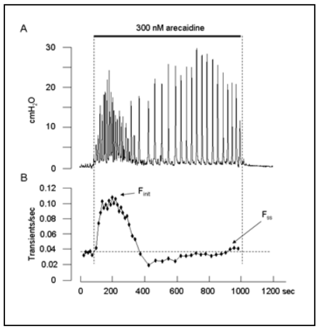
CS Sherrington (1852-1927)

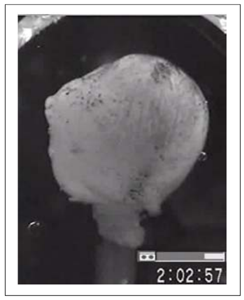
The Concept of Afferent Noise







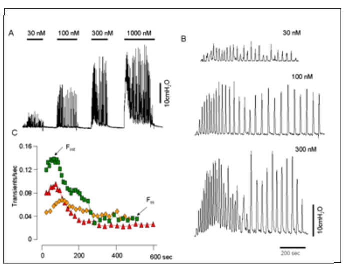




Cholinergic augmentation of autonomous activity in normal bladder

Cholinergic activation of phasic activity in the isolated bladder: possible evidence for M_3- and M_2-dependent components of a motor/sensory system

Steven M. Finney, Laurence H. Stewart and James I. Gillespie*
Western General Hospital, Edinburgh, Scotland and *The Urophysiology Research Group, School of Surgical and Reproductive Sciences, The Medical School, The University, Newcastle upon Tyne, UK



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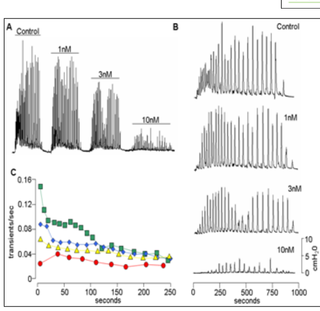
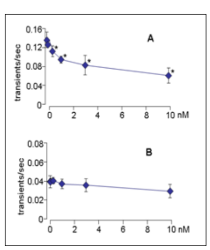
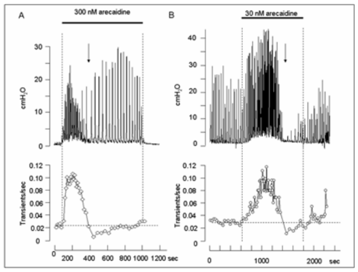
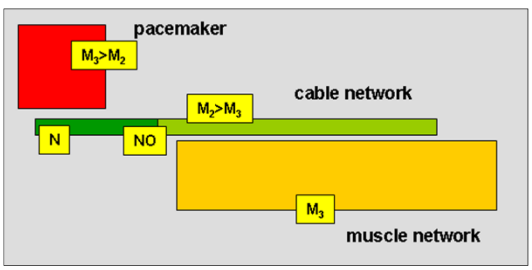




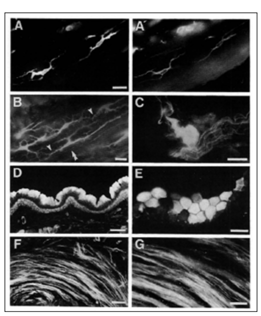
The Overactive Bladder
(obstruction model)





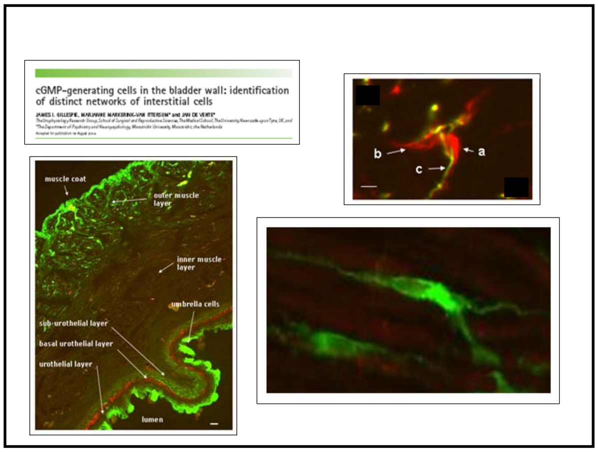
Interstitial cells

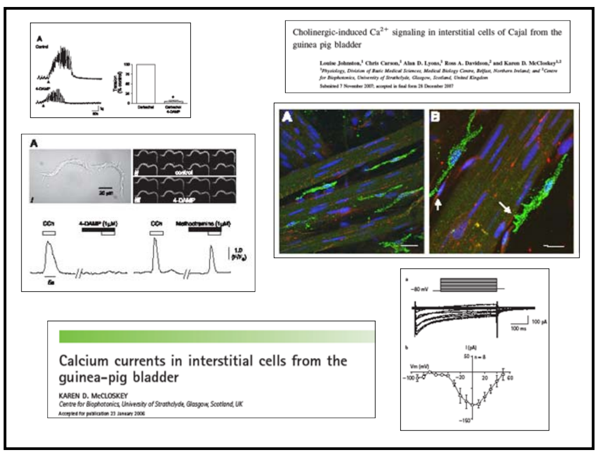
Santiago Ramon y Cajal
(1952-1934)

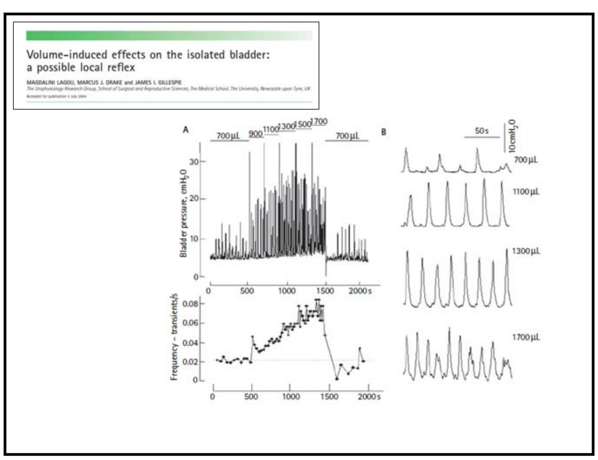


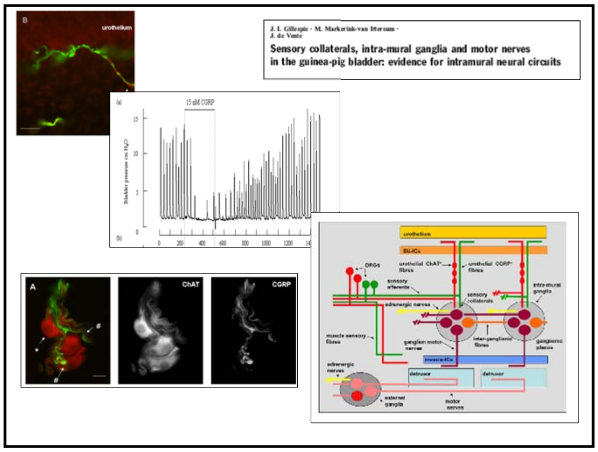
DISTRIBUTION OF NITRIC OXIDE SYNTHASE-IMMUNOREACTIVE NERVES AND IDENTIFICATION OF THE CELLULAR TARGETS OF NITRIC OXIDE IN GUINEA-PIG AND HUMAN URINARY BLADDER BY cGMP IMMUNOHISTOCHEMISTRY

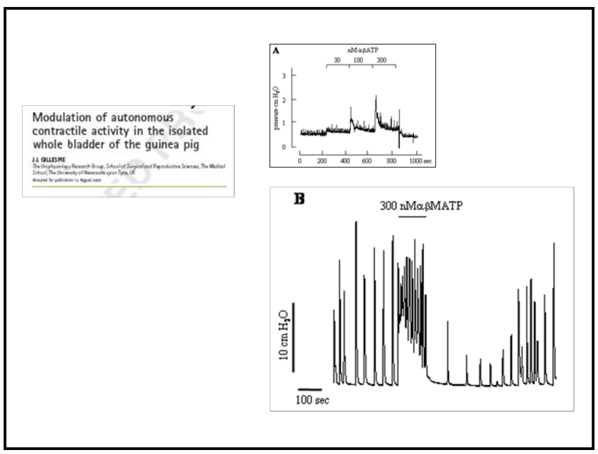
P. J. SMET, J. JONAVICIUS, V. R. MARSHALL and J. DE VENTE

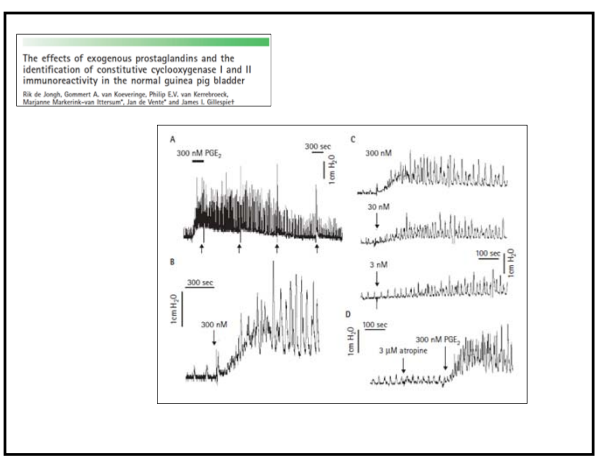

cGMP-generating cells in the bladder wall: identification of distinct networks of interstitial cells
muscle coat
outer muscle layer
inner muscle layer
umbrella cells
sub-urothelial layer
basal urothelial layer
urothelial layer
lumen
b
a
c


Cholinergic-induced Ca2+ signaling in interstitial cells of Cajal from the guinea pig bladder
A
B
Calcium currents in interstitial cells from the guinea-pig bladder
KAREN D. McCLOSKEY
Centre for Biophotonics, University of Strathclyde, Glasgow, Scotland, UK

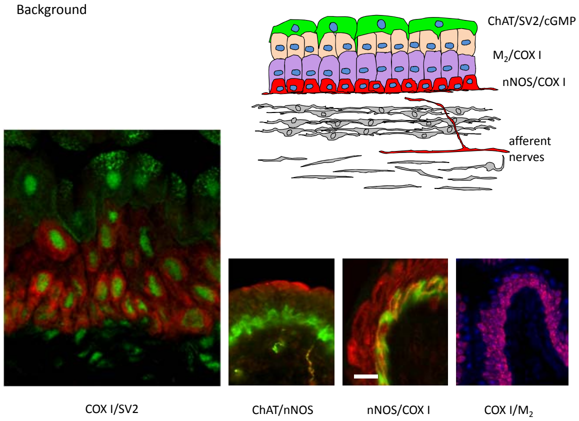

Volume-induced effects on the isolated bladder: a possible local reflex
MAGDALINI LAGOU, MARCUS J. DRAKE and JAMES I. GILLESPIE
A
B
700 μL
Bladder pressure, cmH2O
Frequency – transients/s
50 s
1100 μL
1300 μL
1700 μL


J. I. Gillespie · M. Markerink-van Ittersum · J. de Vente
Sensory collaterals, intra-mural ganglia and motor nerves in the guinea-pig bladder: evidence for intramural neural circuits
urothelium
ChAT
CGRP

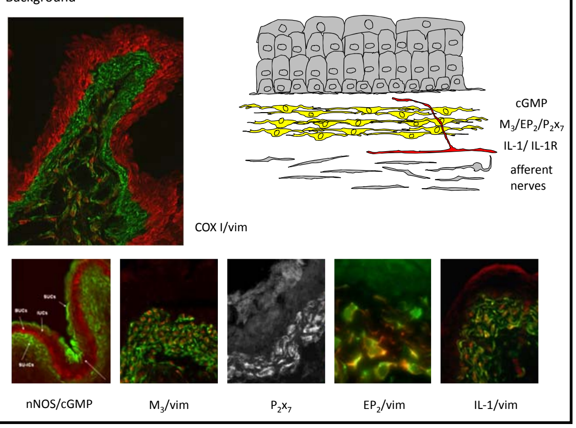

Modulation of autonomous contractile activity in the isolated whole bladder of the guinea pig
J.I. GILLESPIE
A
B
300 nMαβMATP
10 cm H2O
100 sec


The effects of exogenous prostaglandins and the identification of constitutive cyclooxygenase I and II immunoreactivity in the normal guinea pig bladder
Rik de Jongh, Gommert A. van Koeveringe, Philip E.V. van Kerrebroeck, Marjanne Markerink-van Ittersum*, Jan de Vente* and James I. Gillespie†
300 nM PGE2
300 sec
300 nM
30 nM
3 nM
100 sec
3 µM atropine

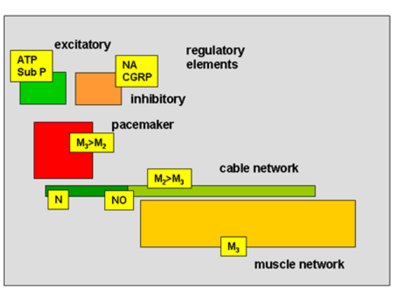
Background

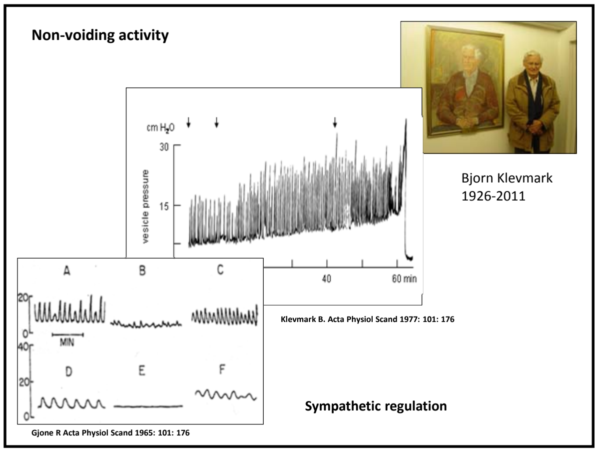


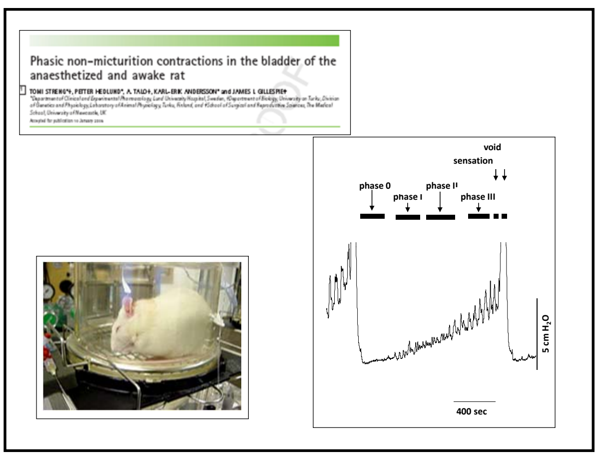
Background

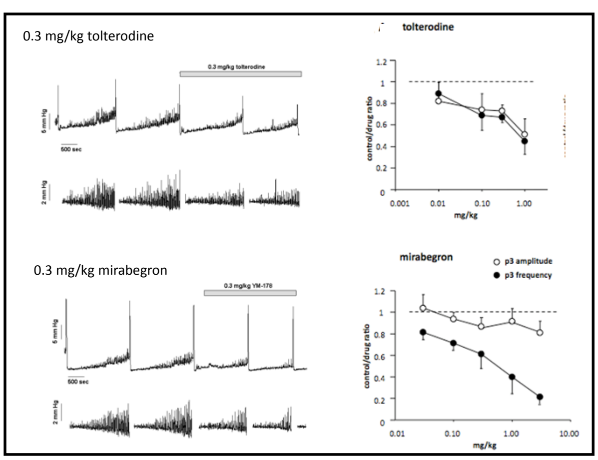


Complex regulation of autonomous activity




Non-voiding activity
cm H2O
30
15
vesicle pressure
40
60 min
Bjorn Klevmark
1926-2011
A
B
C
D
E
F
MIN
Klevmark B. Acta Physiol Scand 1977: 101: 176
Sympathetic regulation
Gjone R Acta Physiol Scand 1965: 101: 176


Phasic non-micturition contractions in the bladder of the anaesthetized and awake rat
void
sensation
phase 0
phase I
phase II
phase III
5 cm H2O
400 sec


0.3 mg/kg tolterodine
tolterodine
control/drug ratio
mg/kg
0.3 mg/kg mirabegron
mirabegron
p3 amplitude
p3 frequency
500 sec
mg/kg

Institute for Medical Research, Durham Veteran's Affairs Medical Center
Division of Urology, Department of Surgery, Duke University Medical Center

The origins and roles of non-voiding bladder contractions

Matthew O. Fraser, Ph.D.

International Continence Society
Workshop W12B
Monday 29th August 2011

1

Autonomous Activity in the Urinary Bladder

- **Lessons from History**
  - Sherrington (1892) reported continued bladder contractile activity in situ following suprasacral spinal cord transection and sacral root denervation in a Rhesus macaque, concluding that, "the rhythmic action of the monkey's bladder arises in its own muscular wall".
  - Bülbring (1957) reported on rhythmicity of potentials from smooth muscle cells of the guinea pig colon (a general smooth muscle ref).
  - Anderson et al. (1972) reported on rhythmicity of potentials from smooth muscle cells of the rabbit bladder.
  - Anderson (1978) reported on rhythmic contractile activity of rabbit bladder strips.
  - Sibley (1984) compared spontaneous contractions in bladder strips from rabbit, pig and human.

2

Autonomous Activity in the Urinary Bladder

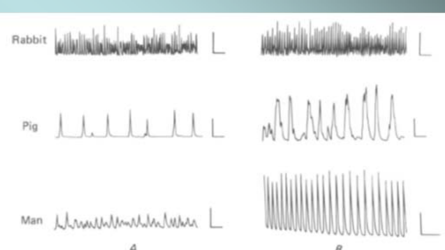


Fig. 1. Spontaneous activity in detrusor muscle strips from rabbit, pig and man. *A*, strips taken from the anterior dome. *B*, strips taken from the trigone in man and pig, and the posterior wall of the rabbit bladder. Vertical bars represent 0·25 g of tension. Horizontal bars represent 1 min.

Sibley GNA. 1984. J. Physiol. 354: 431-443

3

Autonomous Activity in the Urinary Bladder

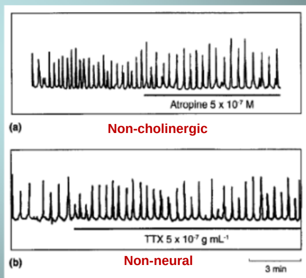


FIGURE 1. *Spontaneous contractile activity of a strip of guinea-pig detrusor. Irregular phasic contractions arise from the baseline. The contractions are not blocked by atropine or tetrodotoxin (TTX), suggesting a myogenic origin.*

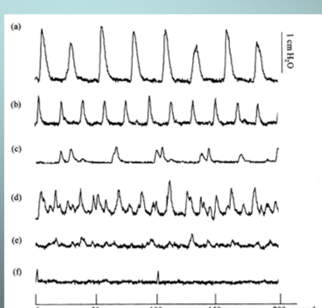
Guinea Pig Bladder Strips

Brading AF. 1997. Urology. 50(Sup. 6A): 57-67

Autonomous Activity in the Urinary Bladder

- **Lessons from History**
  - Coolsaet (1985) and Coolsaet et al. (1993) describe micromotions of the bladder
  - Drake, Harvey and Gillespie (2003) measure micromotions and pressure changes in ex vivo guinea pig preparation, correlate measured micromotions to pressure changes

Autonomous Activity in the Urinary Bladder

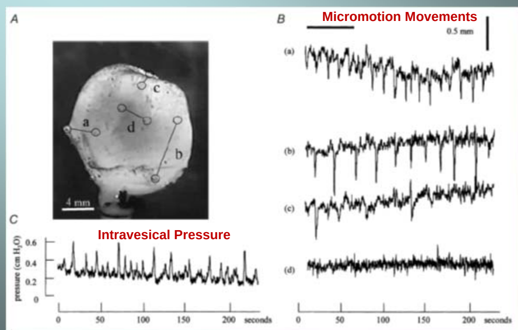


Spontaneous Ex Vivo Bladder Contractions

Figure 1
Spontaneous pressure changes in the freshly isolated whole bladder of the guinea pig. Six sections of recording of intravesical pressure (a–f) are shown, each originating from a different bladder. The abscissa shows time in seconds; the vertical bar shows intravesical pressure in cmH_2O and relates to each record shown. All bladders were maintained in gassed Tyrode solution at 33–34°C. Recordings were made within 30–60 min of killing the animal.

Drake, Harvey and Gillespie. 2003. Exp Physiol. 88:19-30.

Autonomous Activity in the Urinary Bladder



Drake, Harvey and Gillespie. 2003. Exp Physiol. 88:19-30.

7

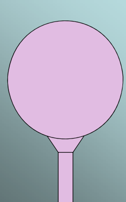
Autonomous Activity in the Urinary Bladder

- **Lessons from History**
  - Denervated bladders in situ, whole mount ex vivo bladders and in vitro bladder strips all demonstrate rhythmic contractile activity that by all appearances is myogenic in origin and not neurogenic

8

LUT Anatomy

- **Bladder Smooth Muscle Anatomy**
  - Variably Defined as having 1 layer with intermeshed multi-oriented muscle fibers to 3 somewhat defined layers (inner + outer longitudinal and middle circular)
    - Depends on species, investigator and region examined



  - Many agree that orientations become more distinct as approach the urethra, especially the longitudinal smooth muscle systems
  - Further, that the inner longitudinal layer continues into the urethra – 1 organ, not 2!
    - Described as extending to mid-urethra or even more posterior
    - Not 2 organs, but 1 – the Vesicourethral muscularis

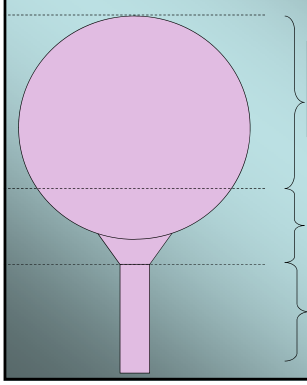
9

LUT Anatomy

- **Bladder Smooth Muscle Anatomy**
  - There are also differences in dorsal vs. ventral surfaces, most notably the trigone, but not limited to that, resulting in regional differences in the presence or absence of circumferential or longitudinal muscle fibers
  - The bladder itself may be subdivided as base and dome, as evidenced by innervation and sensitivity to neurotransmitters rather than by sharp demarcations in smooth muscle anatomy

10

Functional Anatomy of Vesicourethral muscularis



Dome – Compliant reservoir during filling with multidirectionally oriented fibers directed toward central-downward compression during voiding

Base – Receiver and distributer of urine from the ureters during storage and from the dome during voiding. Actively participates in both functions. Activation of circumferential vs. longitudinal layers by function.

Urethra – Outlet with discrete components directed toward storage (circumferential) and voiding (longitudinal)

11

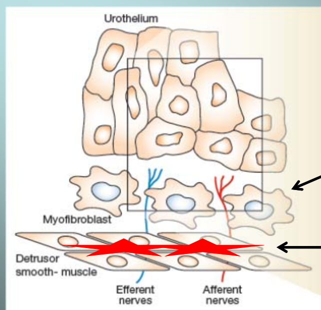
LUT Anatomy

- **Bladder Smooth Muscle Anatomy**
  - The bladder demonstrates functional compartmentalization depending on the role at the time.
    - During filling, it is at least a 2 compartment system, the bladder base and dome (open lumen) and the urethra (closed lumen)
    - Upon micturition, it becomes a 1 compartment system with a single lumen
  - Understanding the role of any myogenic mechanisms will require a better understanding of the smooth muscular cytoarchitecture, including not only the smooth muscle cells themselves, but the ECM (as we heard yesterday) and non-neural signaling cells as well as the interactions of the whole with local and distant neuronal circuitry.

12

LUT Anatomy

- **Transmural Anatomy - Non-neuronal Cellular Network**



ICC
ICC-like
Submucosal
Myofibroblasts
Pacemaker Cells
Fibroblast-cells
Etc., etc. etc.

IC_{IM} – not pacers, modulate/mediate neurotransmission
(Koh, SUFU 110301)

Birder and de Groat. 2007. Nat Clin Pract Urol. 4:46-54.

13

LUT Anatomy

- ***Local*** **Neuronal and Non-neuronal Cellular Network Interaction**

Drake, Mills, Gillespie. 2001. Lancet. 358:401-3.

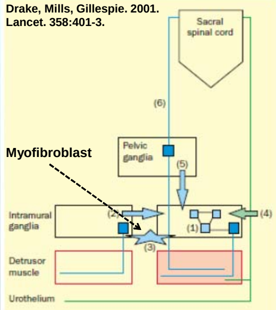


Figure 2: **Detrusor module inputs**

The hypothetical myovesical plexus:

- Made of bladder interstitial cells and nerve ganglia, determines the functional behavior of the bladder wall.

- The basic functional unit is a circumscribed area of muscle, known as a module.

- Each module can contract independently in the right circumstances.

- Activity in neighboring modules can be co-ordinated so that a large proportion of the bladder wall becomes synchronously active.

- Add urothelial signaling with afferent input to ganglia and get one potentially noisy system

14

Normal Utilization of Non-neuronal Networks

- **Given the functional anatomy LUT and dual role of the tissues involved, how might these local peripheral networks be utilized during normal function?**
  – **Bladder Emptying –** This one is easy, coordination of the non-neural networks may allow for a tightly regulated smooth muscle contraction in the detrusor and relaxation of the urethral circumferential smooth musculature.
  – **Bladder Filling** – This one is a little harder to envision mentally, so …

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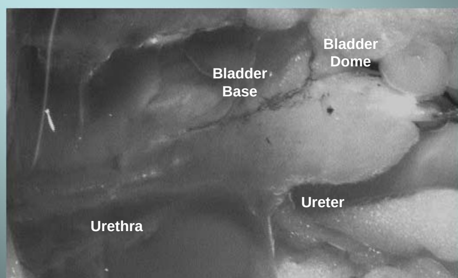
Base-to-Dome Filling Contraction



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Dome-to-Base Non-Voiding Contractions

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Normal Utilization of Non-neuronal Networks

Hypotheses regarding Non-Voiding Contractions

- Dome-to-base non-voiding contractions are due to a spinal reflex in response to stepwise filling in a low compliance and/or irritated bladder – therefore dependent on sacral parasympathetic pathway

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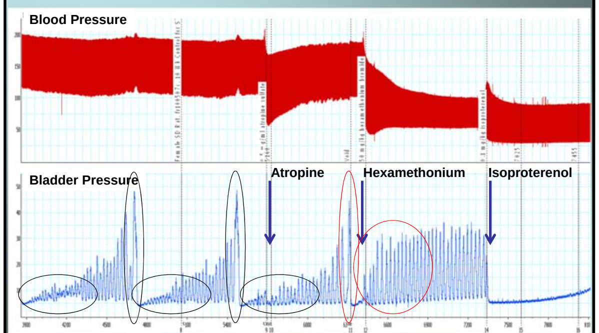
Utilization of Non-neuronal Networks in Aged Rats



Control

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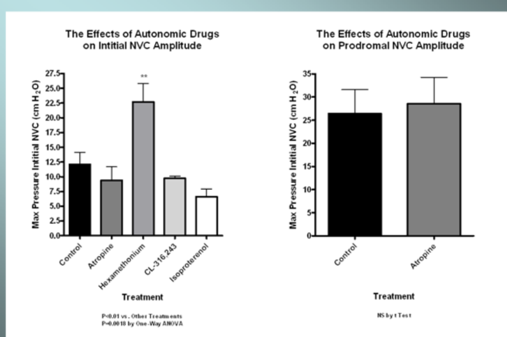
Utilization of Non-neuronal Networks in Aged Rats



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Normal Utilization of Non-neuronal Networks

Hypotheses regarding Non-Voiding Contractions

- Base-to-dome filling contractions are normal part of bladder filling and are a continuation of ureteric filling peristaltic waves, probably summated within and distributed to the detrusor by the trigone – thus not dependent upon neurotransmission
  - **Still Good, Hexamethonium and Beta Agonist results suggest tonic inhibitory modulatory role for sympathetics**

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Normal Utilization of Non-neuronal Networks

Hypotheses regarding Non-Voiding Contractions

- Dome-to-base non-voiding contractions are due to a spinal reflex in response to stepwise filling in a low compliance and/or irritated bladder – therefore dependent on sacral parasympathetic pathway

  – Lack of Hexamethonium effect suggests that spinal reflex is not involved in these experiments, may be myovesical plexus.
  – Lack of Atropine effect suggests that if it is myovesical plexus, it is not via ACh, but perhaps purinergic.
  – If not myovesical plexus, may be continuation of propagated filling contraction electrical wave, traversing the apex of the dome - Beta Agonist data is not inconsistent with this.

  – Finally, it just may be the case that these rats are not true “angry peanuts”, and that these data do not reflect spinal reflex dependent upon parasympathetic circuitry.

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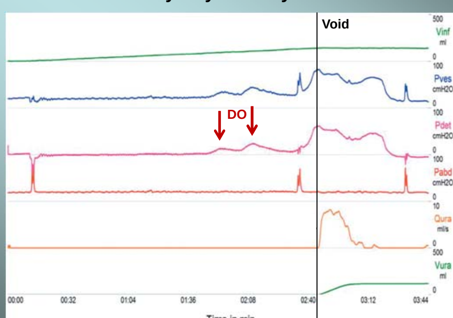
Clinical Correlates

- **Detrusor Overactivity - Cystometry**



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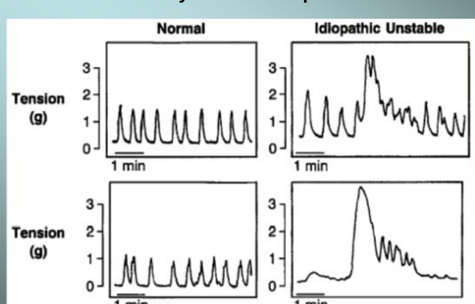
Modified from Panicker and Fowler. 2010. Pract Neurol 10:178-185.

Clinical Correlates

- **Detrusor Overactivity – in vitro strips**

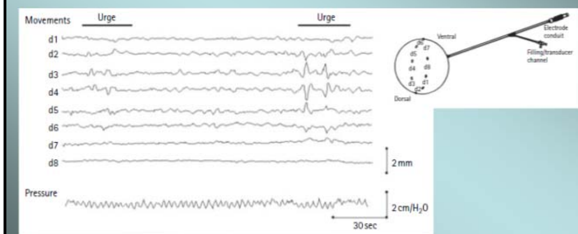


24

Brading AF. 1997. Urology. 50(Sup. 6A): 57-67

Clinical Correlates

- **Urgency**
  - Women with increased sensation of filling had more micromotions than those that did not, and urgency was accompanied by regional (= modular?) micromotor activity



Drake et al. 2005. 1997. BJU International 95: 1002-1005

25

Clinical Correlates

- **Urgency**
  - Micromotions may cause significant afferent effects by stretching surrounding areas even if no total intravesical pressure change. Areas of higher compliance may absorb the pressure impact of modular contraction

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Conclusions

- **Bladder instability and OAB Wet and Dry**
  - Ample evidence suggesting myogenic activity may result in changes in bladder muscle wall tension, which would result in changes in afferent input, with or without changes in overall pressure, and that this may be the source of urgency sensations in some patients with OAB
  - This is not to say that spinal reflex activity is also not a possible factor in some patients with OAB.

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Conclusions

- **New therapeutic strategies?**
  - That anticholinergics and nerve blockers do not block myogenic activity in vitro suggests that smooth muscle relaxant approaches, such as spasmolytics , K-channel openers and beta agonists may work better for patients with myogenic predominant OAB, as long as those treatment do not interfere with the myogenic filling process.
  - Patients with neurogenic predominant OAB may do better with approaches that target afferent pathways. In this regard, it is of interest that most antimuscarinics on the market have ion channel blocking capabilities which may contribute to afferent inhibition.
  - A truly pure parasympathetic efferent blocking approach may not be a good idea, unless the underlying pathology includes spurious (non-reflexive) parasympathetic activity during filling
  - Of course, mixed cause OAB may also exist and may benefit from combination therapy approaches.

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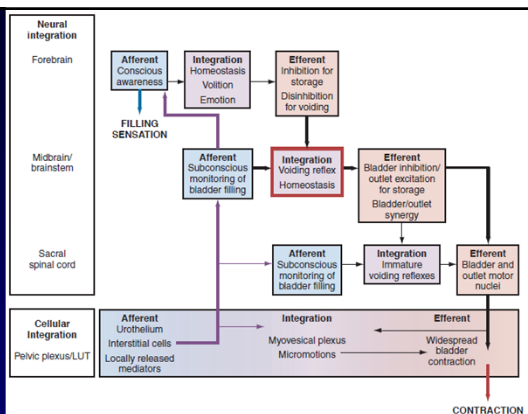
Clinical relevance of non-micturition bladder activity

Marcus Drake
Bristol Urological Institute

Clinical contexts

- Normal bladder filling and voiding
- OAB/ DO
- Impaired filling compliance
- DUA
- PVR



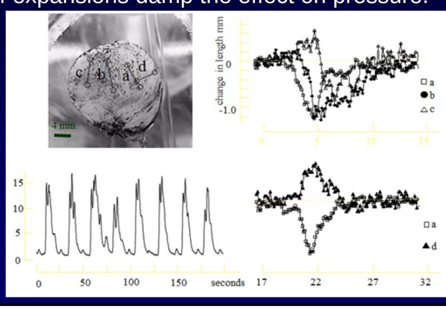
Drake MJ. Campbell Walsh urology 10th edition

Bladder function and dysfunction

- Ability to sense state of bladder filling without change in detrusor pressure
- Overcoming variation in the outlet resistance
- Completeness of bladder emptying

Putative role of MMs in normal LUT

- “Report” filling state; localised distortion stimulates stretch receptors, and configures to volume.
- Mini-expansions damp the effect on pressure.

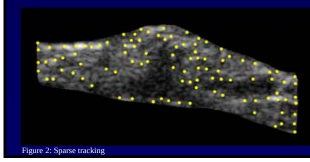


Are NMCs seen in humans?

- Perception that NMCs are not present
  - By definition a bladder contraction during filling constitutes detrusor overactivity (DO)
- Measurement conditions affect observation
  - Stress influences ability to reproduce symptoms
  - Higher prevalence of “DO” in ambulatory testing (Bristow and Neal, 1996)
  - Rate of filling influences compliance (Schafer et al., 2002)

Ultrasound for MMs?

- Transabdominal U/S can pick up interfaces within the detrusor muscle



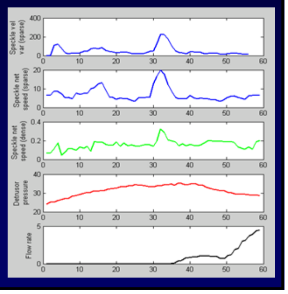
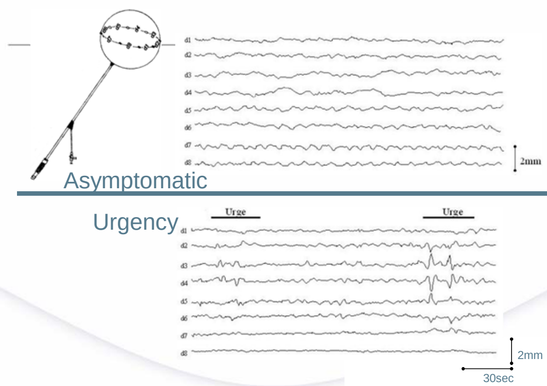


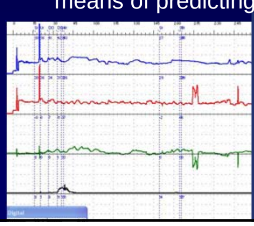
Figure 2: Sparse tracking

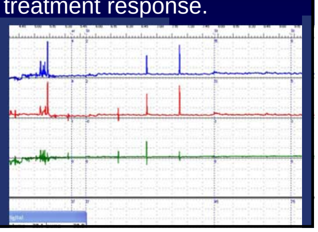


Drake et al. BJU Int 2005; 95: 1002 - 1005

MMs in human OAB

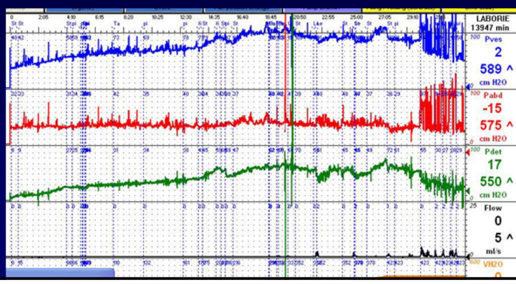
- Higher amplitude MMs in some people with OAB- increased filling sensation without DO. May define a subgroup of OAB patients, providing an objective biomarker and a means of predicting treatment response.

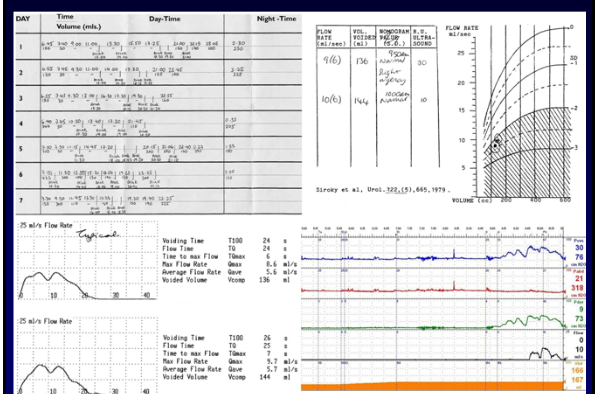




Storage phase properties

1. Compliant (detrusor cells, propagation, elastic)
2. Sensory with intermittent sensation
3. Configured for voiding at any volume



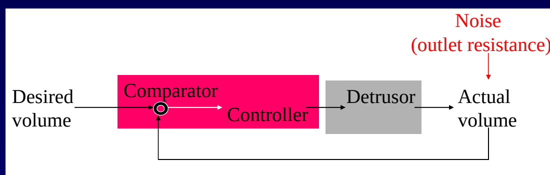


Voiding phase

- ➔ Central command module
- ➔ Peripheral servo
  - – Plant
  - – Comparator

Voiding phase

- PMC sends the permissive command
- Periphery delivers contractile response until comparator sees actual volume matches the desired volume



Drake MJ. Ann Roy Coll Surg Eng 2007

Outlet resistance

- Change in position
- Prostatic enlargement
- Partial urethral occlusion

Voiding dysfunction

- Central command failure
- Peripheral servo failure
  - Plant- impaired detrusor contraction
  - Comparator- failure to detect actual volume or failure to sustain detrusor contraction
- DUA; hesitancy, poor flow and PVR

Bladder properties

Voiding
- Initiation
- Synchronisation
- Contraction
- Perpetuation
- Termination

Storage
- Compliance
- Sensory/ sensation
- Configuration

Both phases
- Co-ordination (synergy)
- Homeostasis