Neuro-urology: Physiology and Pathophysiology of Micturition

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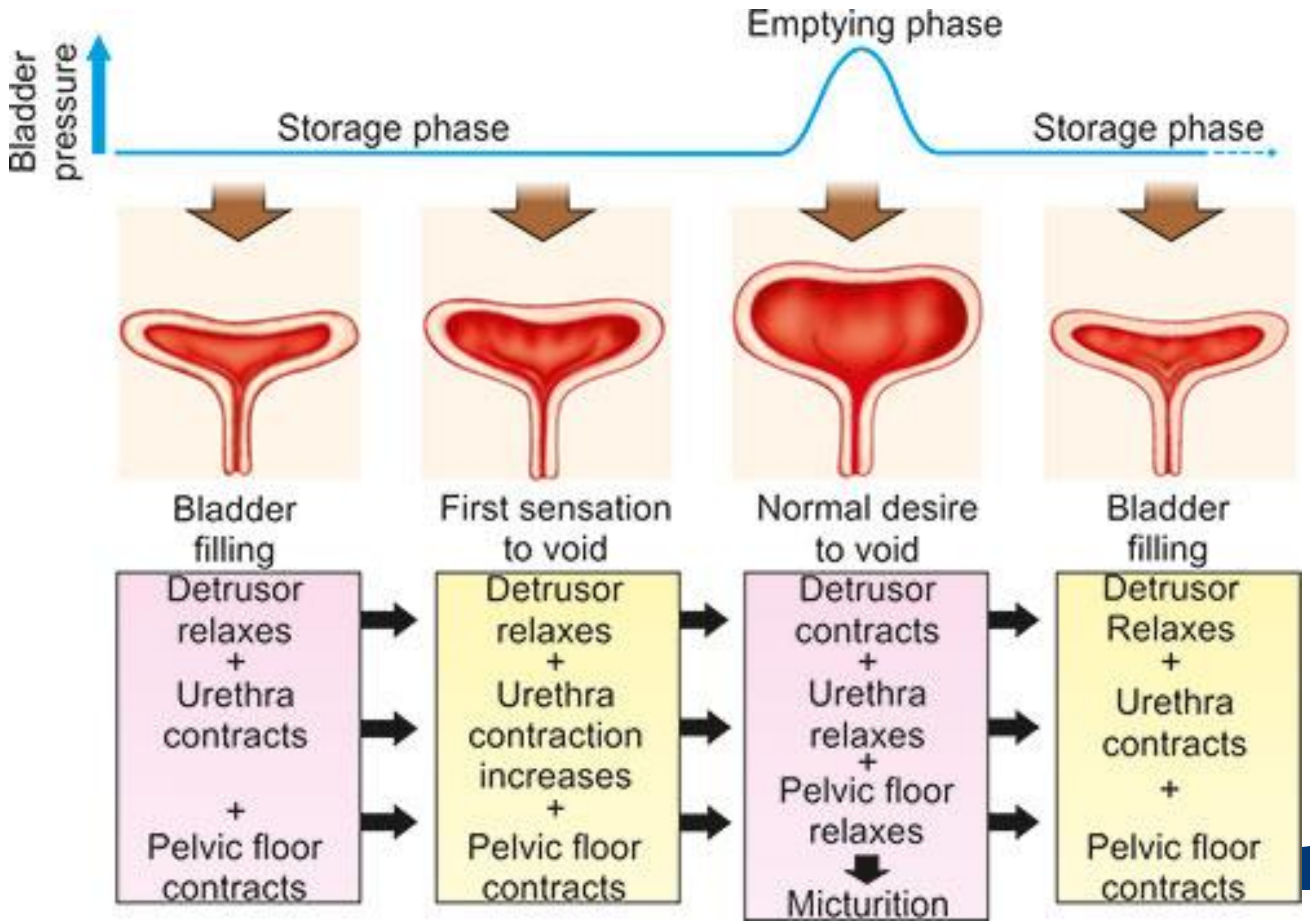
A reminder of 2 basic bladder functions: Storage and Voiding

Two basic phases:

1) Storage/filling -> normal compliance of bladder wall allows storage of urine at low bladder pressures

2) Voiding/emptying -> detrusor contraction with bladder neck and external urethral sphincter relaxation

Allows complete emptying at low pressure with minimal outflow resistance



(from Shweta and Swadhin Manual on Urogynecology)

Evolution of Normal Micturition Control

- During 2-3 years of life there is progressive development towards a socially conscious continence = active learning process

- Natural evolution of micturition control mechanisms depends on an intact neural pathway and awareness of social norms, as well as multiple factors including:
  - 1) Gradual increase in functional bladder storage capacity
  - 2) Maturation of voluntary control of urethral sphincter
  - 3) Progressive development of volitional control over bladder-sphincteric-pelvic floor complex so that child can voluntarily initiate or inhibit micturition reflex

Micturition: By the Years

- Final steps usually achieved by 3-5 years of age:
  - 1-2 years = initial sensation of bladder fullness but unable to postpone micturition
  - 2-3 years = can delay micturition for short time
  - 3-4 years = can start micturition even when bladder not full; beginning to have nocturnal continence
  - 4-5 years = can voluntarily interrupt ongoing voiding

Evolution of Normal Micturition Control

- Traditional believed that micturition in newborns and infants occurs automatically with full bladder by simple spinal cord reflex

- **<u>CK Yeung et al (Br J Urol 1995)</u>**
  - Studied neonates and infants with cystometry and/or polysomnography
  - Micturition NEVER occurred during quiet sleep
  - Voiding often … n
  - Evidence con… inal reflex with an uninhibited bl…
  - Also suggests … ss not primary delay in matu…

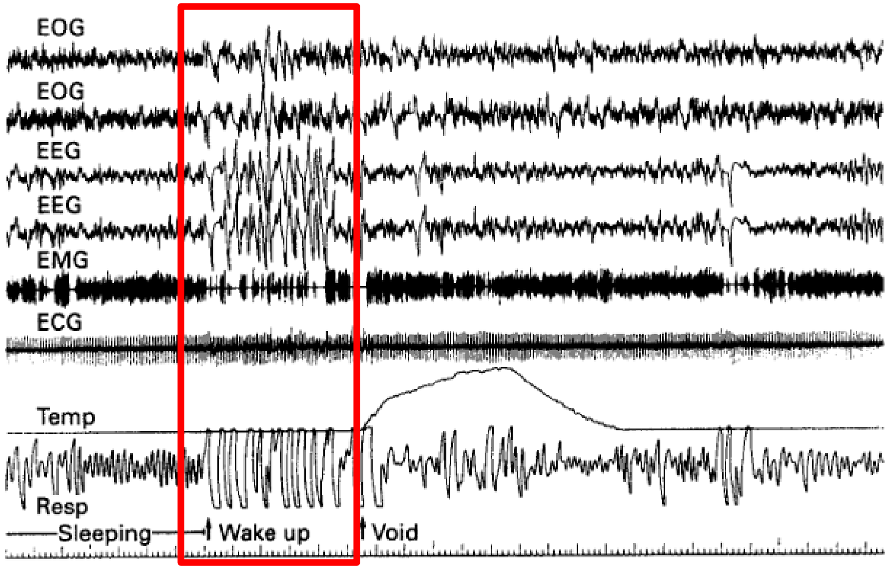


Fig. 3. Polysomnographic recording showing the changes in EEG, EOG, ECG and respiration rate as the infant awoke (arrow) and cried. Voiding (indicated by the temperature rise) followed shortly afterwards.

© 1995 British Journal of Urology 76, 235–240

Evolution of Normal Micturition Control

- **Micturition** more complex even in newborns and modulated by higher neural centers
- Additional studies on fetuses also suggest that micturition rarely, if ever, occurs during sleep
  - “Fetuses don’t wet the bed”
  - During sleep bladder is quiescent and stable

Transitory Detrusor-Sphincter Dis-coordination in Infancy

- Urodynamic findings show association with high voiding pressures and interruption of urine flow but with no impairment of overall bladder emptying
  - Voiding pressures in infant males > females
  - U Sillen et al, J Urol 1996 -> 125 vs 69 cmH20
  - Similar findings from CK Yeung et al, Br J Urol 1995

- These high detrusor pressures mainly observed during first year of life and decrease progressively with age (U Sillen et al, J Urol 1996)
- Interrupted or “staccato” type pattern of urinary stream seen in over half of infants -> due to detrusor-sphincter discoordination

- This period of dysfunction resolves with successful toilet training
- Therefore, one must be cautious in the assessment of young children with apparent voiding dysfunctions and resist the temptation to over interpret intermittent or transient symptoms as pathologic

Changes in Functional Parameters

- **Voiding frequency**
  - Peaks at 2-4 weeks of life = once per hour
  - Declines by 6-12 months = 10-15x per day
  - Continues to decline by 2-3 years = 8-10x per day
  - By age 12 = voiding pattern that of normal adult = 4-6x per day
- **Bladder capacity**
  - Increases with growth of child
  - Adequate reservoir function for urine storage is necessary to meet the increased rate of urine production and decreased voiding frequency

Koff equation

- Bladder capacity (mL) = [Age (yrs) + 2] x 30

ICCS equation

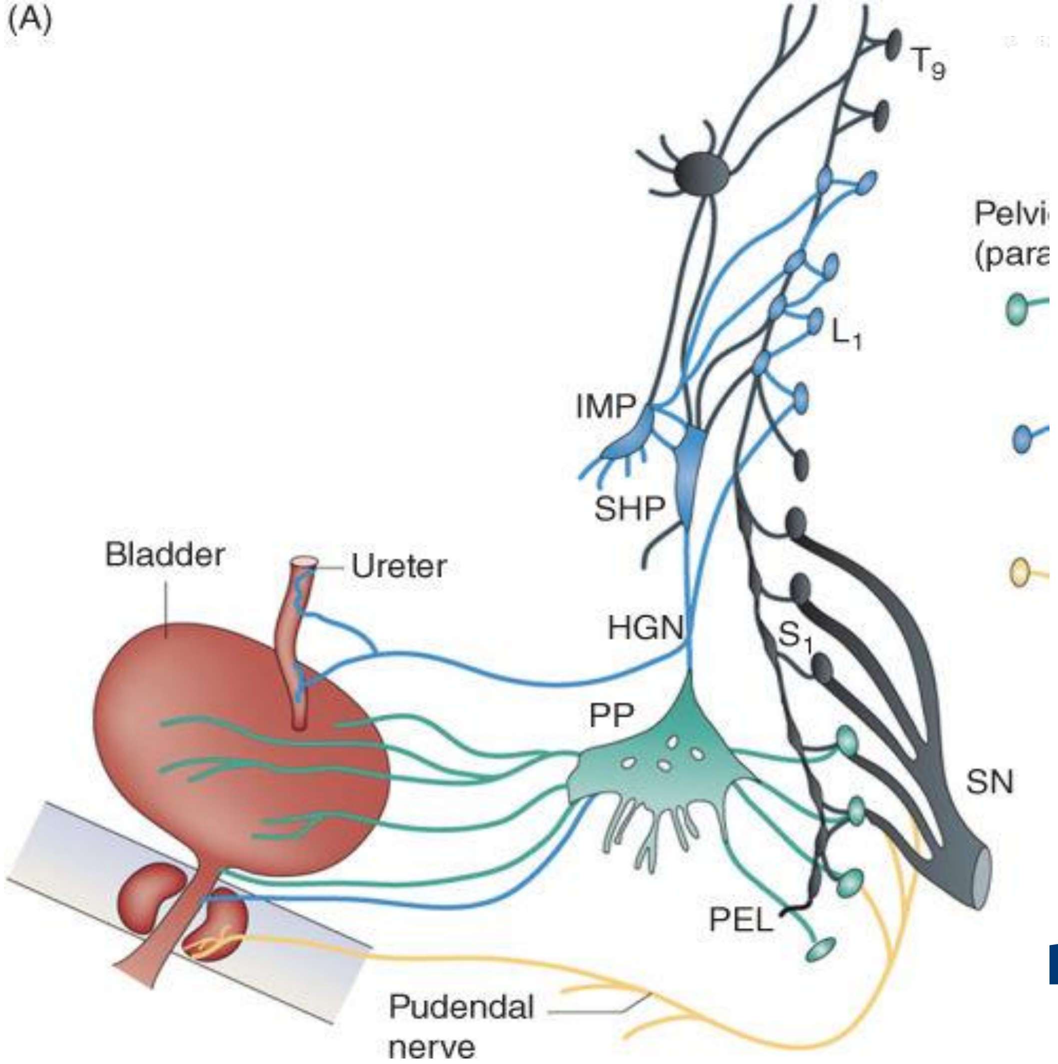
- Bladder capacity (mL) = [Age (yrs) + 1] x 30

For infants <2 years old:

- Bladder capacity (mL) = 7 x weight (kg)

Two phases of bladder function:
Storage (continence) and emptying (micturition)

- Complex integrated network:
  - Central nervous system (brain, brain stem, spinal cord)
  - Peripheral nervous system (autonomic, somatic)
  - Bladder smooth muscle (detrusor)
  - Interstitial stroma (collagen and elastin)
  - Lamina propria
  - Urothelium
  - Urethral smooth muscle
  - Pelvic floor striated muscles
  - External urethral sphincter



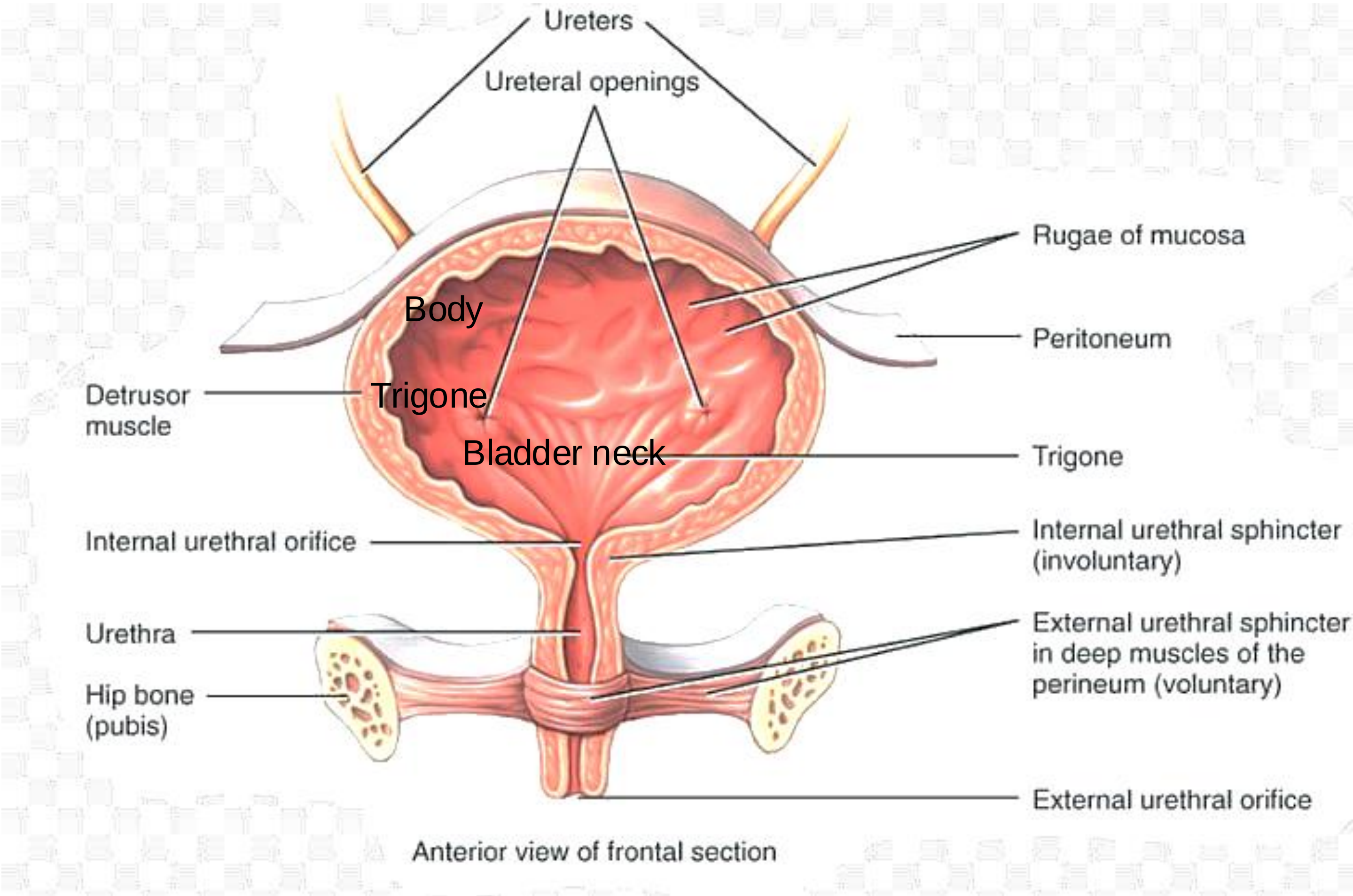
(De Groat et al, Comp Physiol 2015)

Bladder Anatomy

- **<u>Abdominal organ</u>**
  - Easily palpable when full in infants and children

- **<u>Body vs. Base</u>**
  (trigone and bladder neck)

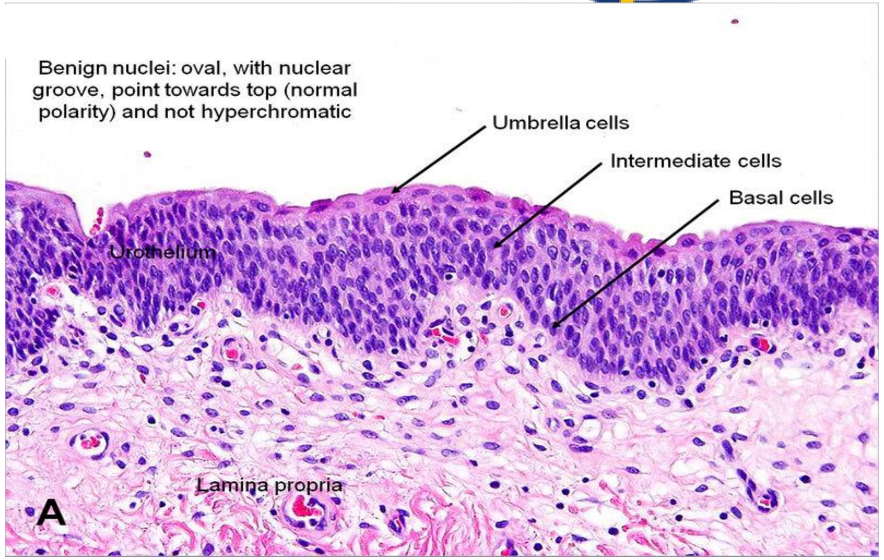
- **<u>Bladder wall</u>** (3 layers):
  - Mucosa – urothelium
  - Detrusor – meshwork of smooth muscle
  - Adventitia



(from ar.europeanwriterstour.com)

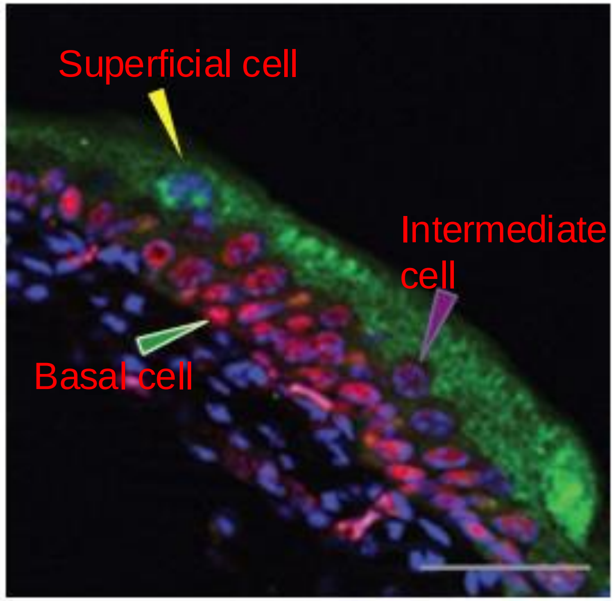
Bladder storage: Role of the urothelium

- Urothelium = multilayered specialized epithelium of three cell types
- Superficial cells = umbrella cells
  - Large, multinucleated cells that can expand
- **Often overlooked but has important physiologic functions**:
  - 1) Barrier layer (impermeability) -> uroplakins and tight junctions
  - 2) Highly innervated –> afferent signaling, “sensory organ”
  - 3) Prevent bacterial adherence (GAG)



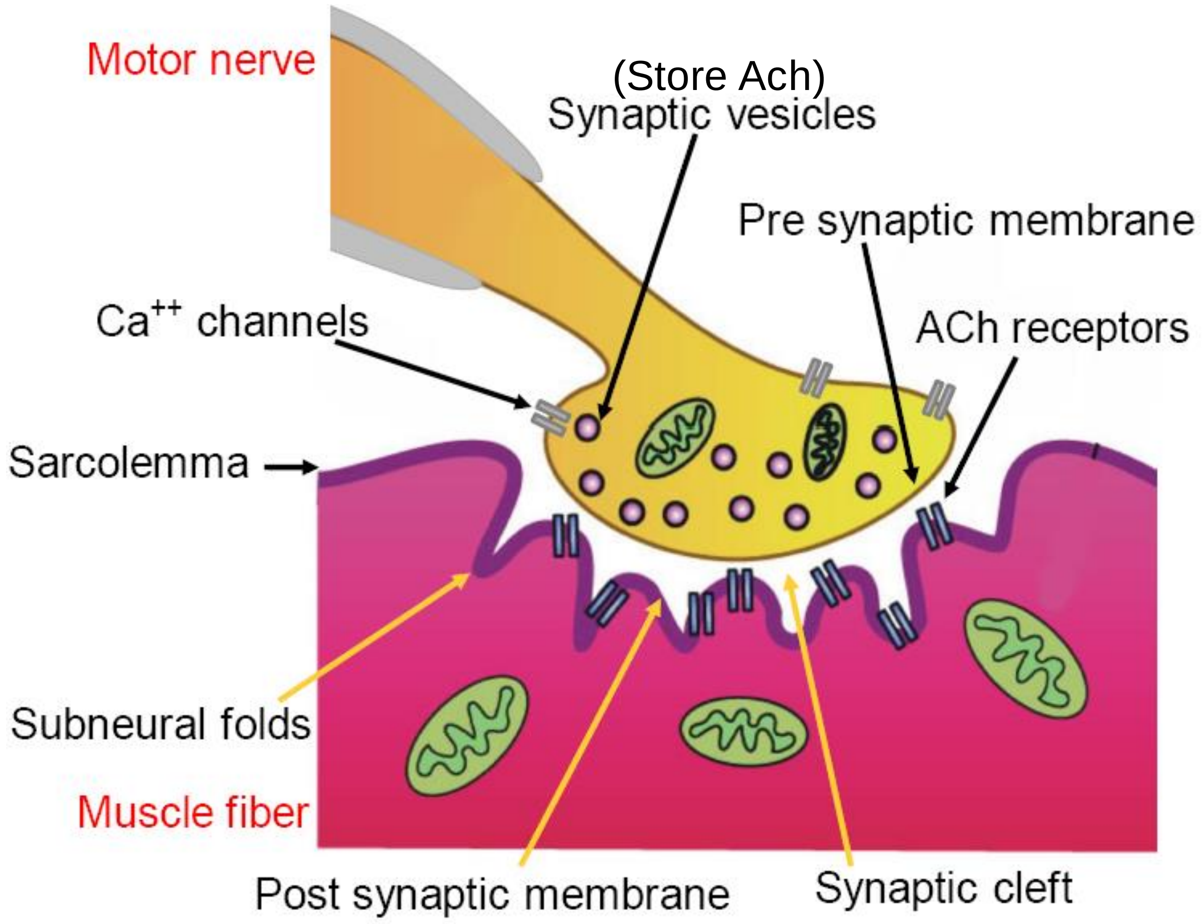
(from https://www.ncbi.nlm.nih.gov/books/NBK540963/figure/article-18355.image.f2/)

Pharmacologic target: Intravesical instillation of medications to increase GAG layer (DMSO, hyaluronic acid, heparin) or block afferent sensory nerve activity (resiniferatoxin) have been studied in patients with chronic cystitis/bladder pain



(from Van Batavia et al, Nat Cell Biol, 2014)

Bladder muscle: Detrusor and the neuromuscular junction

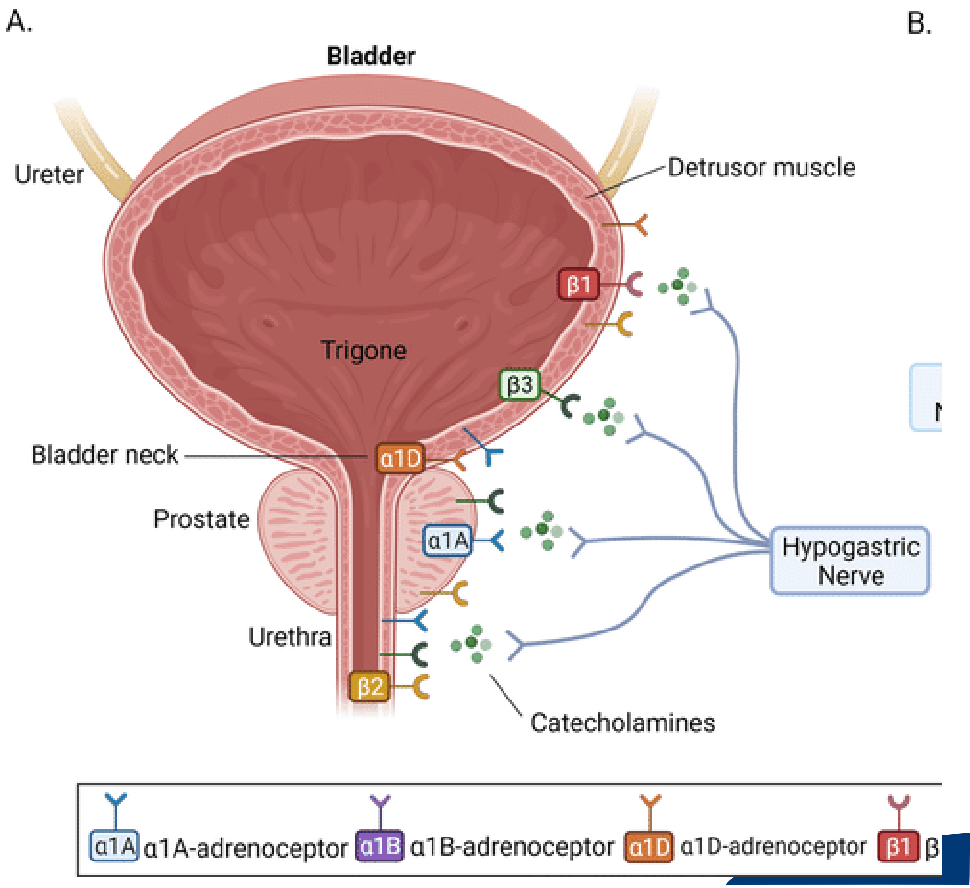


- Detrusor is **smooth muscle**
- Autonomic innervation
- Function is regulated by motor neurons as well as local paracrine factors (many released by the urothelium)
- Parasympathetic neurons release acytelcholine (ACh) which activates **muscarinic receptors** on detrusor muscle
  - 5 subtypes of muscarinic (M) receptors
  - M_2 receptor most common in bladder, but **M_3 receptor mediates detrusor contraction**

Two urinary sphincters to remember

- Both have role in urinary continence by closure of bladder neck and proximal urethra

- 1) Internal urinary sphincter (ie, bladder neck) = smooth muscle fibers from bladder base and trigone which traverse inferiorly though bladder neck towards proximal urethra
  - High concentration of **alpha-adrenergic receptors (α1A > α1D?)** at bladder neck and urethra
  - **During micturition – bladder base, bladder neck, and proximal urethra contract simultaneously as a unit to produce a funneling effect that opens up the bladder outlet with initiation of voiding**
  - **Delay or failure to open appropriately = bladder neck dysfunction**

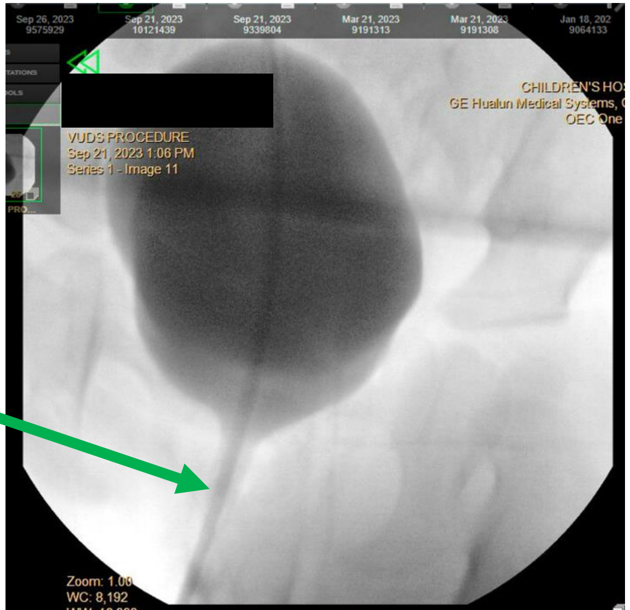


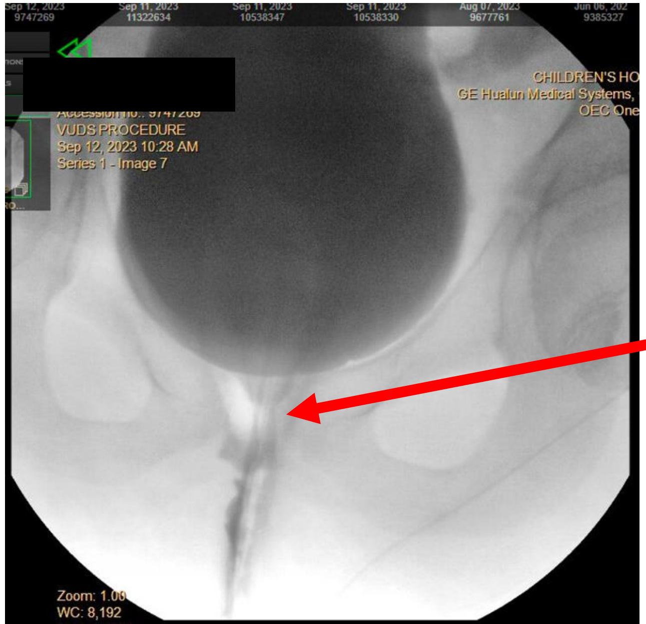
(from Archer et al Cell Comm & Signaling, 2021)

Two urinary sphincters to remember

- <u>2) External urinary sphincter</u> = cylindrical structure which is accentuated anteriorly and thin or absent posteriorly -> horseshoe or omega shape
  - Inner layer of smooth muscle
  - Outer layer of striated muscle
  - **First step in volitional voiding is relaxation of external urethral sphincter**
  - **Dyssynergy between detrusor contraction and external sphincter relaxation can lead to:**
    - **Detrusor-external sphincter dyssynergy (DESD)**
    - **If DESD is voluntary = dysfunctional voiding**

Open EUS

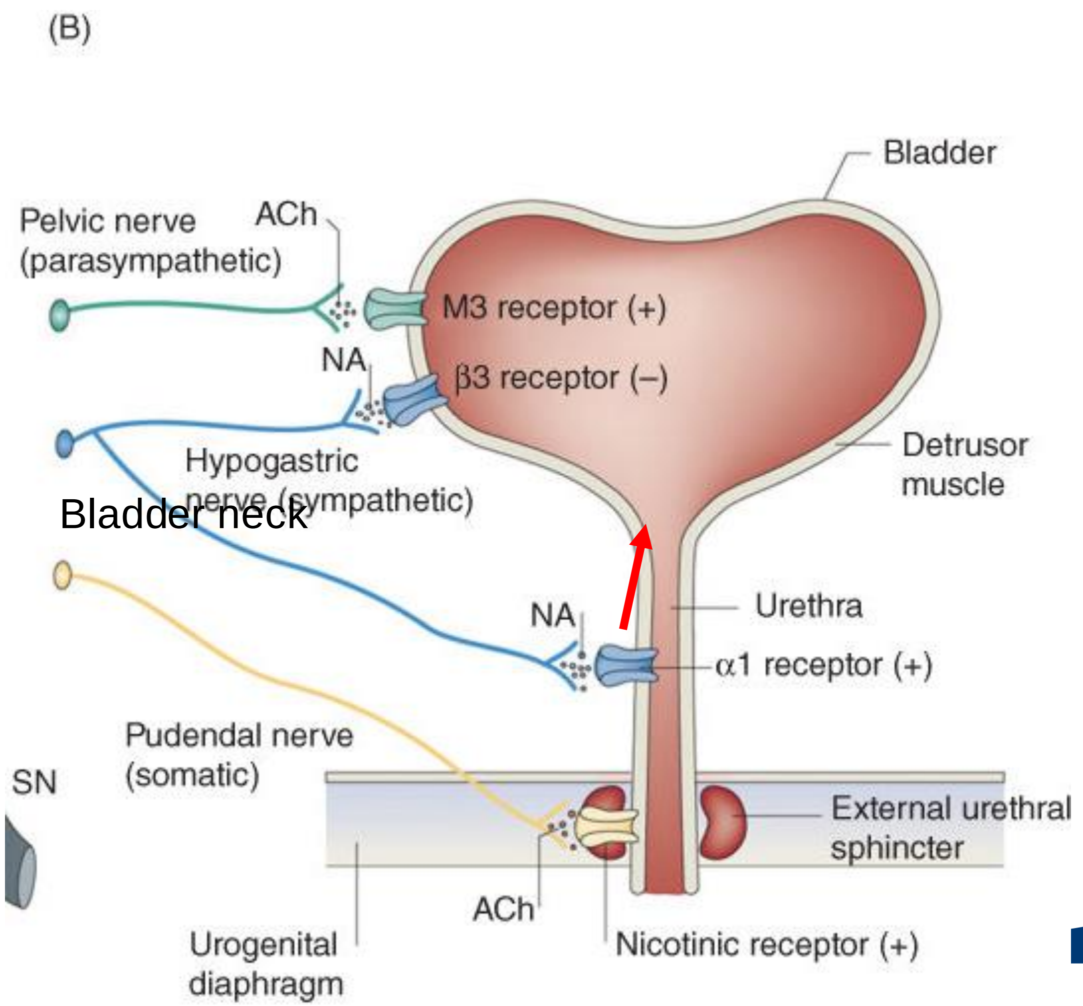




Closed EUS during voiding

Neuro-urology: Three nerves to remember

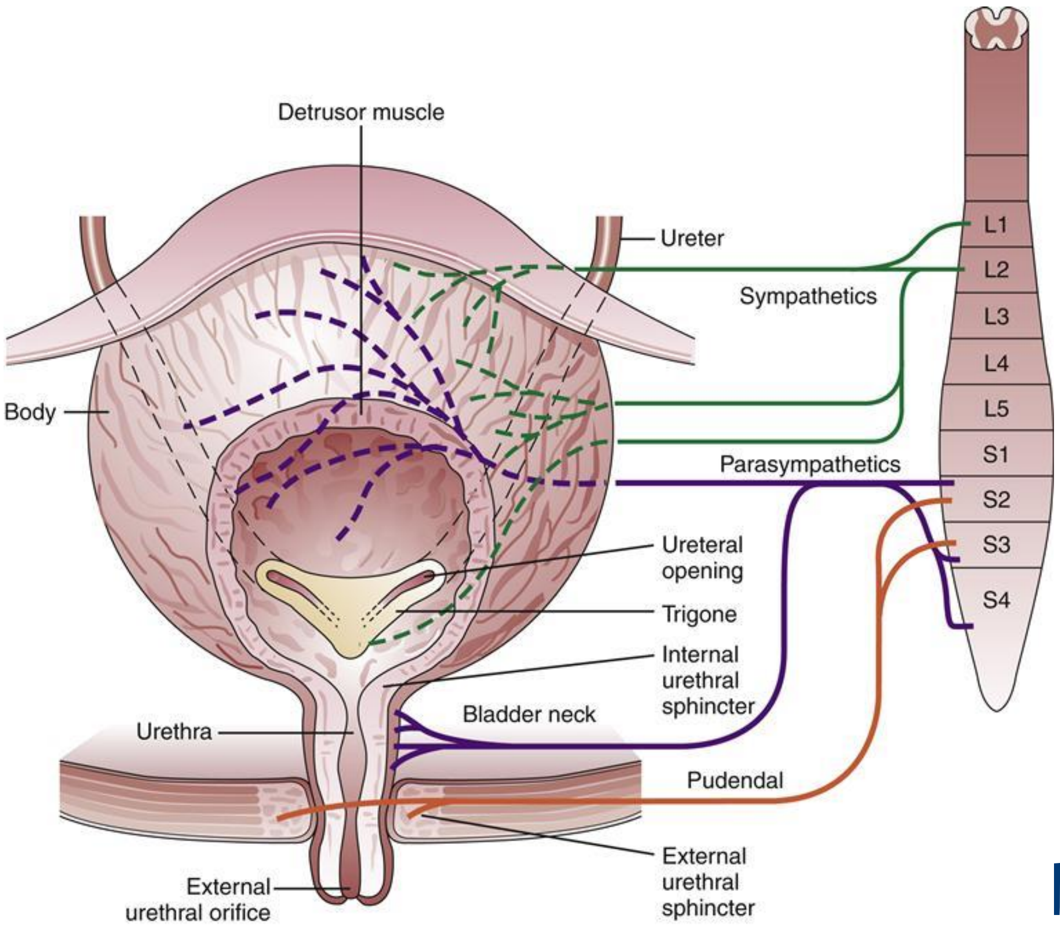
- <u>1) Pelvic nerve (S2-S4)</u> -> sacral parasympathetic nerves -> excitatory input to bladder smooth muscle
- <u>2) Hypogastric nerve (T11-L2)</u> -> sympathetic nerves -> inhibitory input to bladder smooth muscle and excitatory input to bladder neck/urethra
- <u>3) Pudendal nerve (S2-S4)</u> -> sacral somatic nerves -> innervate striated muscle of urethral sphincter and pelvic floor



(De Groat et al, Comp Physiol 2015)

Neuro-urology: Don’t forget afferent nerves!

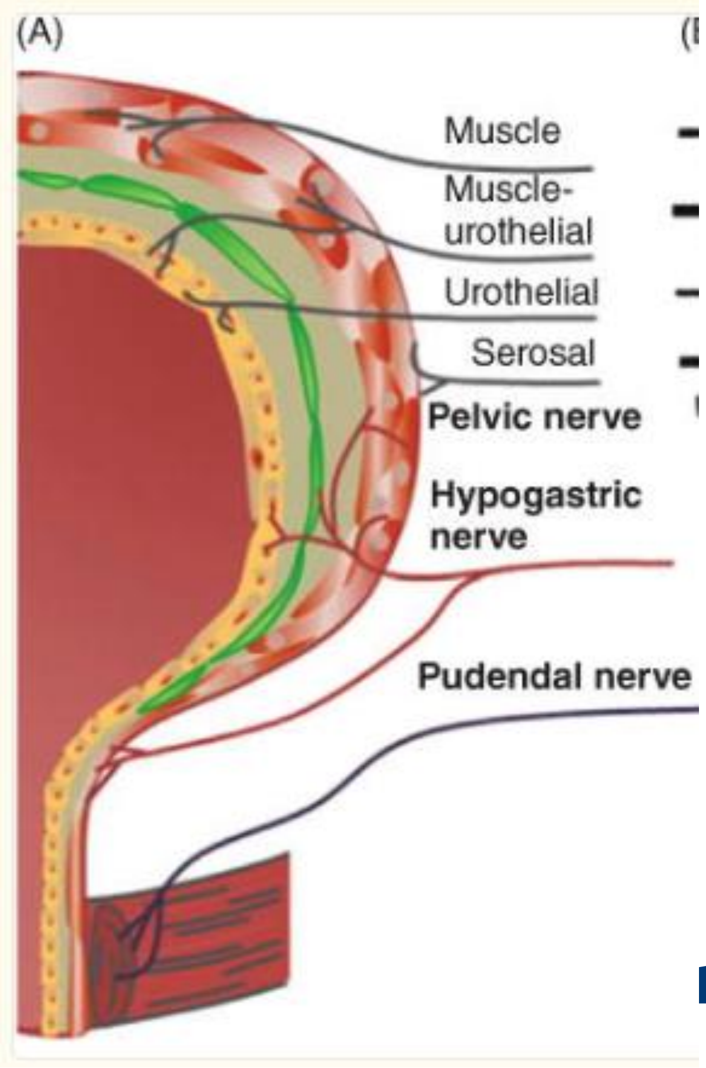
- Afferent nerves travel through the same nerves that carry efferent signals to the bladder (mixed peripheral nerves)
- Found in all layers of the bladder including urothelium (highest concentration = base)
- Sensory information via afferent nerves serve many roles:
  - 1) monitor bladder volume and pressure during storage
  - 2) Alert CNS that it is time to void
  - 3) monitor bladder contraction amplitude during voiding
- Abnormal afferent signaling can lead to LUT symptoms such as urgency and pain



Neuro-urology: Types of Afferent neurons

- **Roles of afferent nerves:**
  - Mechanoreceptors
  - Chemoreceptors
  - Silent (20-25%)

- **Two types of afferent neurons:**
  - **Aδ fibers (myelinated)**
    - 1/3 of bladder afferent fibers
    - Most in detrusor smooth muscle
    - Primary mechanosensitive fiber in LUT
  - **C fibers (unmyelinated)**
    - More widespread distribution (urothelium)
    - Some are “silent” mechano-insensitive -> can become mechanoreceptive in response to noxious stimuli



(De Groat et al, Comp Physiol 2015)

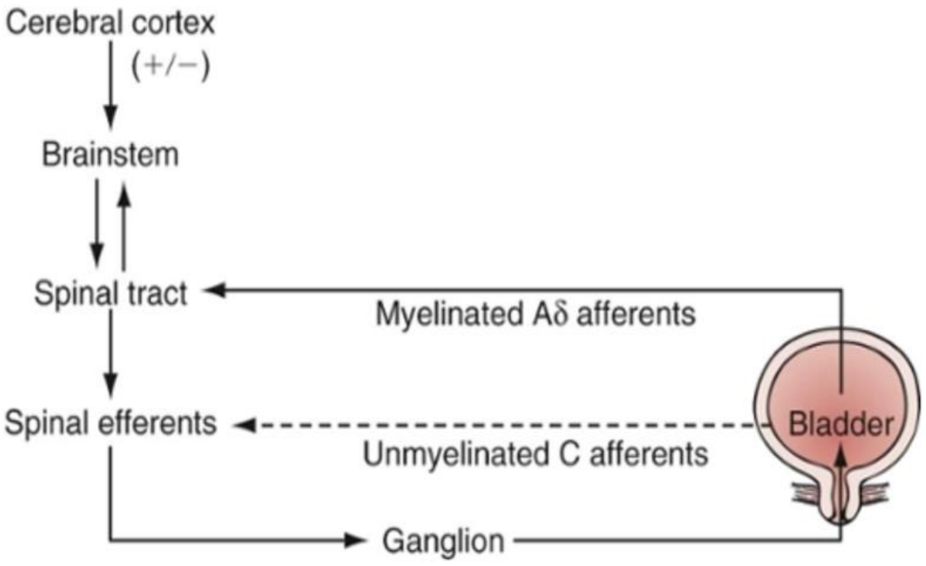
Neuro-urology: Types of Afferent neurons

TABLE 69-2 Bladder Afferent Properties

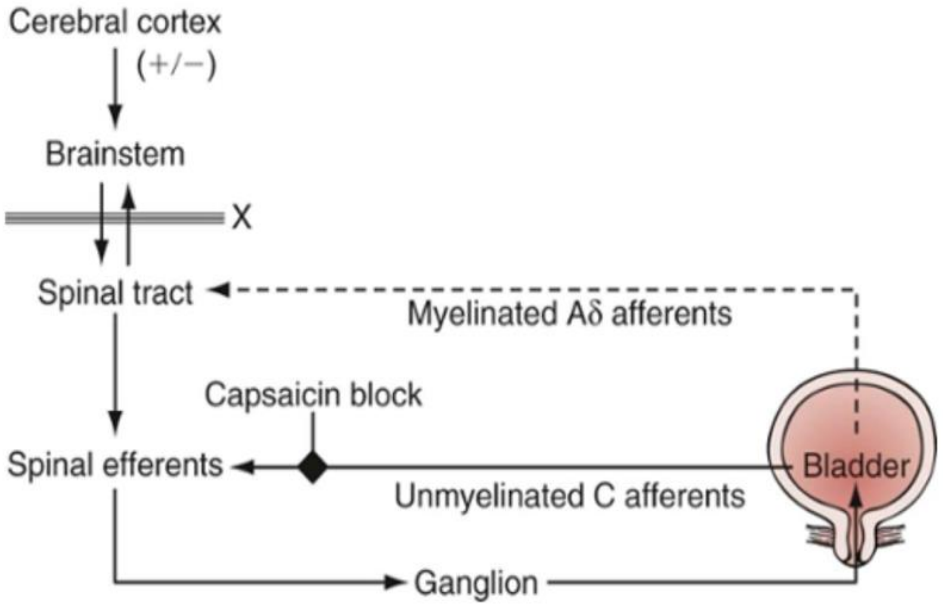
FIBER TYPE	LOCATION	NORMAL FUNCTION	INFLAMMATION EFFECT
Aδ (finely myelinated axons)	Smooth muscle	Sense bladder fullness (wall tension)	Increase discharge at lower pressure threshold
C fiber (unmyelinated axons)	Mucosa	Respond to stretch (bladder volume sensors)	Increase discharge at lower threshold
C fiber (unmyelinated axons)	Mucosa muscle	Nociception to overdistention	Sensitive to irritants
		Silent afferent	Become mechanosensitive and unmask new afferent pathway during inflammation

(From: Dmochowski, Alan Wein, Louis Kavoussi, Alan Partin, Craig Peters, R. *Campbell Walsh Wein Urology - Electronic*. Available from: Elsevier eBooks+, (12th Edition). Elsevier - OHCE, 2020)

- **Normal micturition reflex**
  - **Aδ fibers** respond to bladder filling
  - As bladder fills, in series recruitment of **Aδ fibers** leads to strong sense of urgency
  - **C fibers** mostly silent



- **Pathologic conditions**
  - Neurologic diseases, aging, inflammation
  - **C-fibers** become predominant to **Aδ fibers**
  - Aberrant afferent pathway signaling via C-fibers leads to urinary urgency, incontinence, and/or bladder pain



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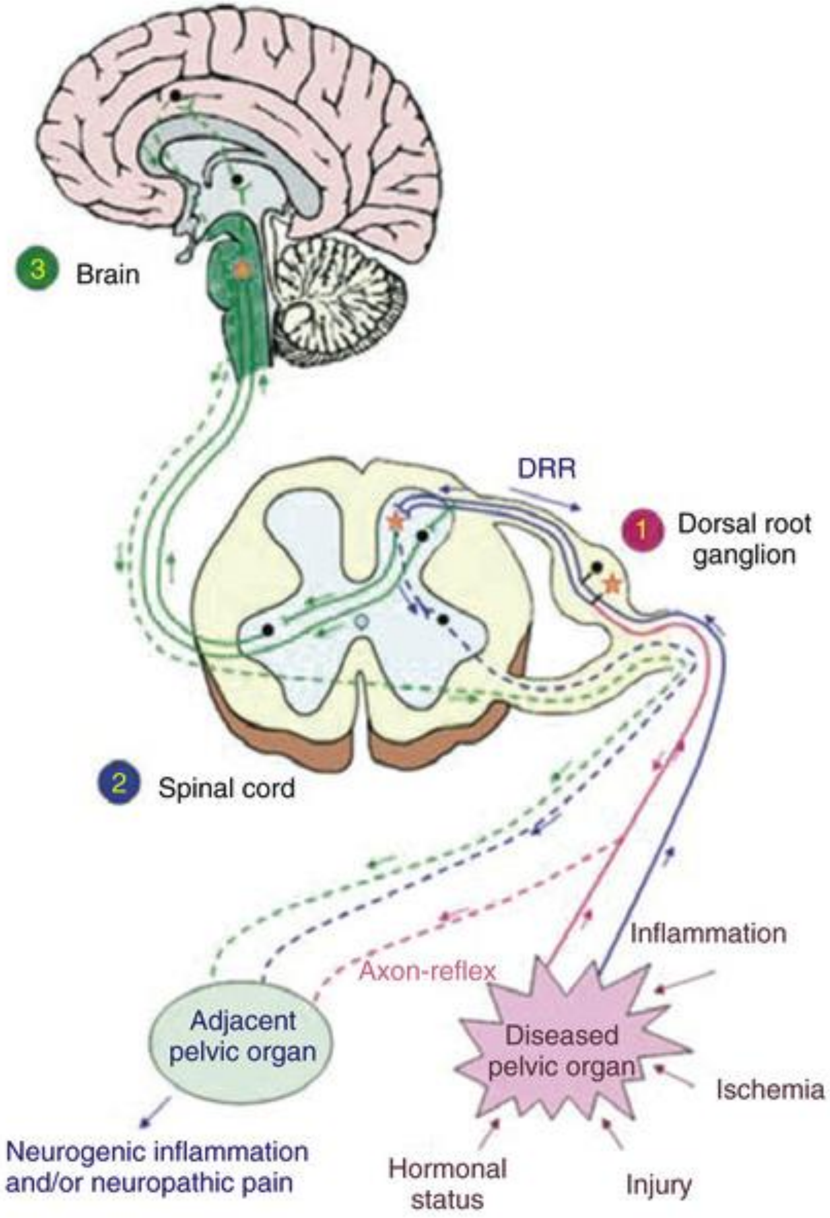
Pelvic Organ Interaction: Bladder/Bowel Cross-talk



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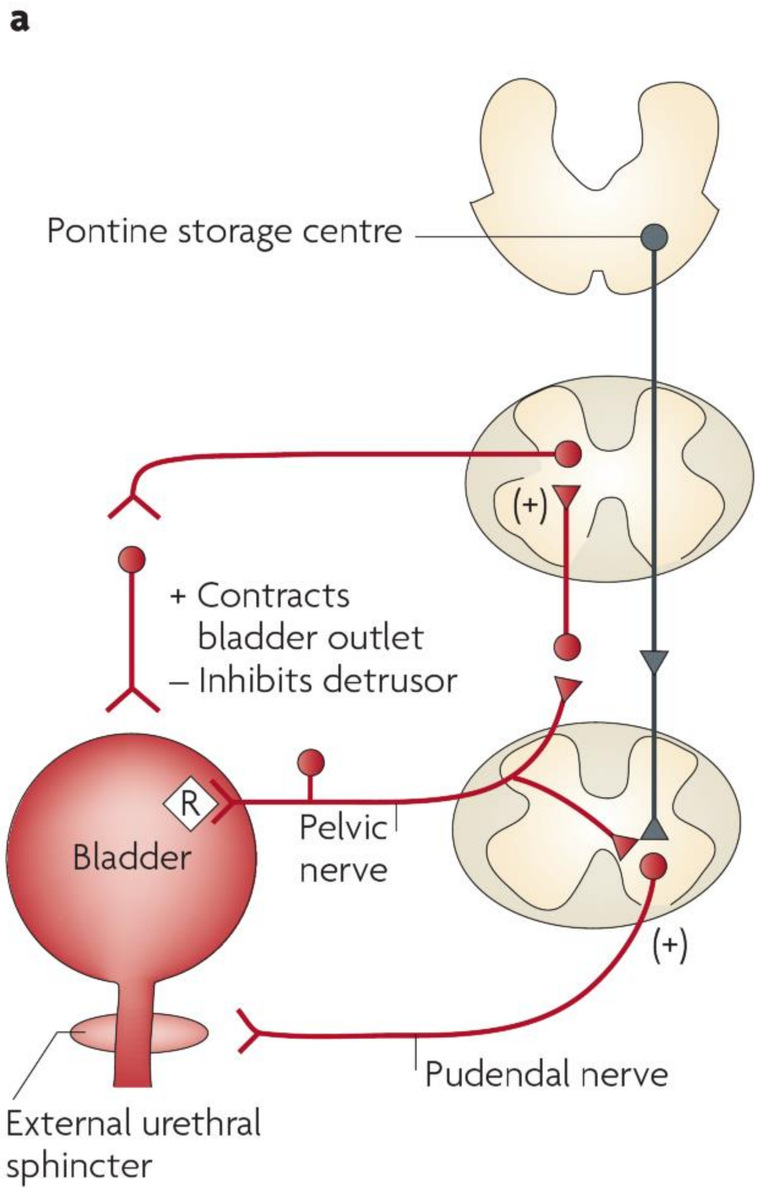
Basic Lower Urinary Tract Reflexes

- **Urine storage reflex (guarding reflex)**
  - Spinal reflex pathway
  - Distention of bladder -> low level bladder afferent activity (via parasympathetic pelvic nerve to spinal cord)
  - Stimulates sympathetic outflow via hypogastric nerve
    - Contraction of bladder neck and proximal urethra (Alpha-receptors)
    - Inhibits contraction of detrusor muscle (Beta-3 receptors)
  - Stimulates pudendal (somatic) nerve outflow
    - Contraction of external urethral sphincter (nicotinic receptors)



(from Fowler et al Nat Review Neuroscience 2008)

Basic Lower Urinary Tract Reflexes

- **Voiding/Micturition Reflex**
  - Spinobulbospinal reflex
  - Increased distention of bladder -> high level bladder afferent activity (via parasympathetic pelvic nerve to supraspinal regions/brainstem)
  - Supraspinal/brainstem activity (likely coordinated by the pontine micturition center) leads to:
    - Stimulation of parasympathetic outflow via pelvic nerve
      - Contraction of detrusor muscle (muscarinic receptors)
    - Inhibition of sympathetic outflow via hypogastric nerve
      - Relaxation of bladder neck and proximal urethra (alpha-receptors)
    - Inhibition of pudendal (somatic) nerve outflow
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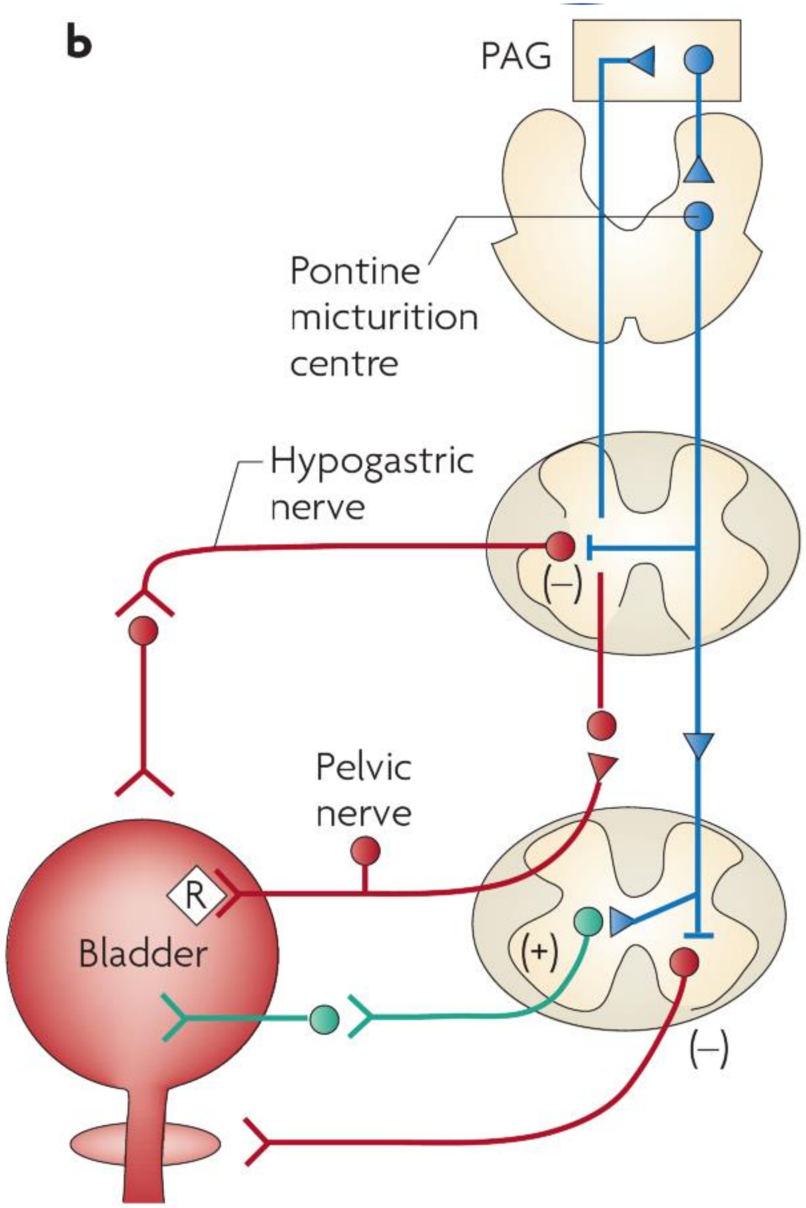


(from Fowler et al Nat Review Neuroscience 2008)

Pharmacotherapy of lower urinary tract

Parasympathetic

- **Anti-muscarinics**
  - Oxybutynin*
  - Tolterodine*
  - Darifenacin
  - Solifenacin*
  - Trospium
  - Atropine
  - Glycopyrrolate

Sympathetic

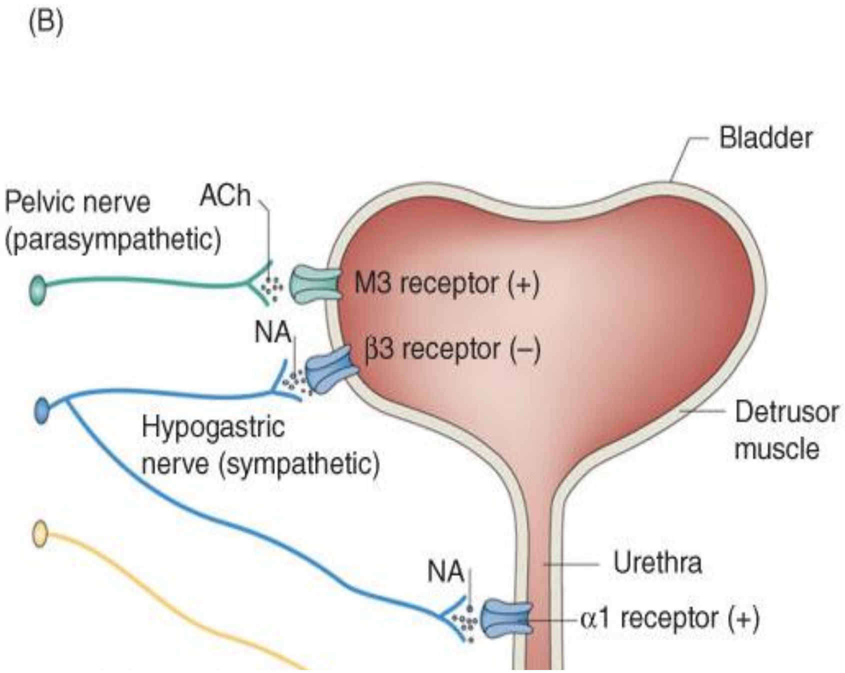
- **α-1 selective blocker**
  - Tamsulosin
  - Doxazosin
  - Terazosin

β3-adrenoreceptor agonist

- Mirabegron
- Vibegron
- Solabegron

Simple way to think about LUT receptors

- **Bladder body**:
  - Muscarinic receptors (M3, M2) -> **PARASYMPATHETIC** -> detrusor contraction and sensory function
    - Anti-muscarinics
  - Beta-3 receptors -> **SYMPATHETIC** -> detrusor relaxation and ?sensory function
    - Beta-3 agonists



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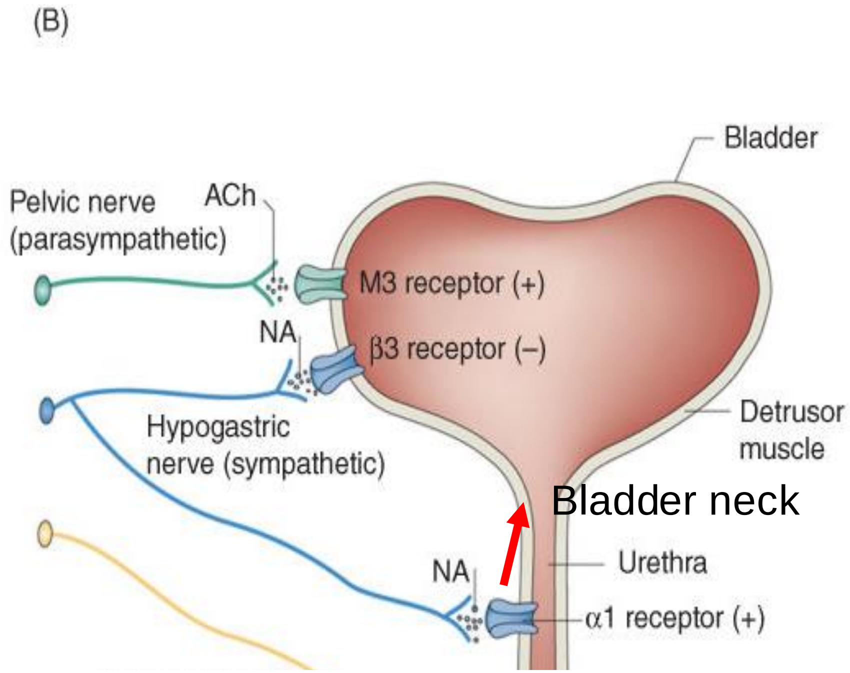
- **Bladder neck**:
  - Alpha1-receptors (1a, 1d) -> **SYMPATHETIC** -> bladder neck contraction/closure
    - Alpha1-blockers (antagonists)



Simple way to think about LUT receptors

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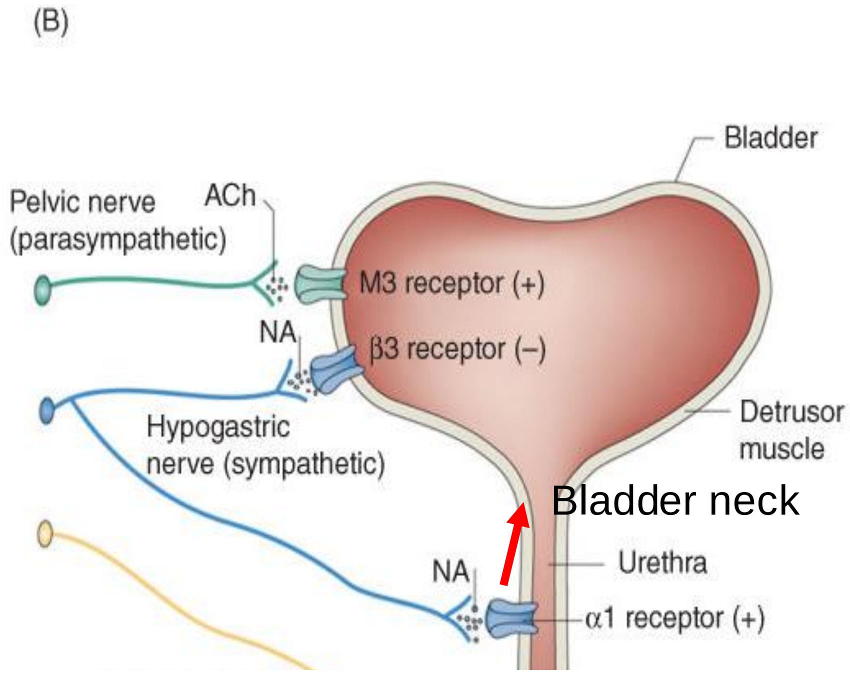
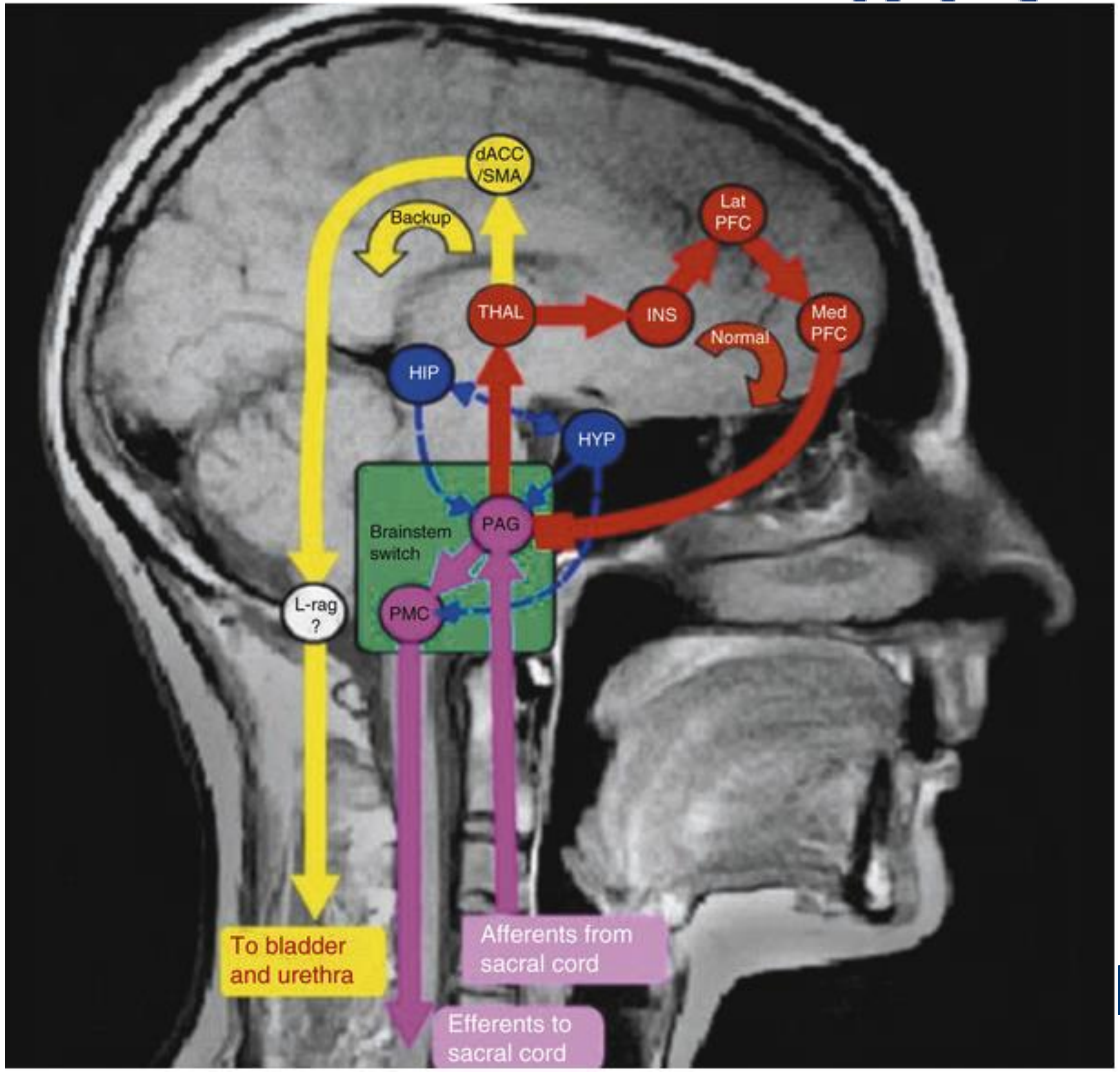
- **Bladder neck**:
  - Alpha1-receptors (1a, 1d) -> **SYMPATHETIC** -> bladder neck contraction/closure
    - Alpha1-blockers (antagonists)
- **Urethra**:
  - Alpha1-receptors (1a, 1d) -> **SYMPATHETIC** -> urethral contraction/closure
    - Alpha1-blockers (antagonists) -> ?DESD
    - Alpha1-agonists -> theoretical role for stress urinary incontinence



Supraspinal Pathways

- Anatomic and physiologic studies in animals
  - Brainstem
    - Dorsal pons = "command center for micturition"
      - Barrington's nucleus
      - Pontine micturition center (PMC)
    - Locus ceruleus (LC)
- Human brain imaging studies (SPECT, PET, fMRI)
  - Thalamus
  - Hypothalamus (pre-optic area)
  - Insula
  - Anterior cingulated gyrus
  - Periaqueductal gray
  - Prefrontal cortex



Conclusions

- Normal bladder function involves complex interplay between may systems to regulate storage and micturition reflexes
- There are clear differences in micturition parameters in infants which should “normalize” by 4-5 years when bladder capacity increases, voluntary control of the external urethral sphincter develops, and bladder-sphincter coordination prevails
- Knowledge of bladder anatomy and neuronal pathways is necessary to understand mechanism of action of commonly used bladder dysfunction pharmacologic agents

THANKS

Questions???

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