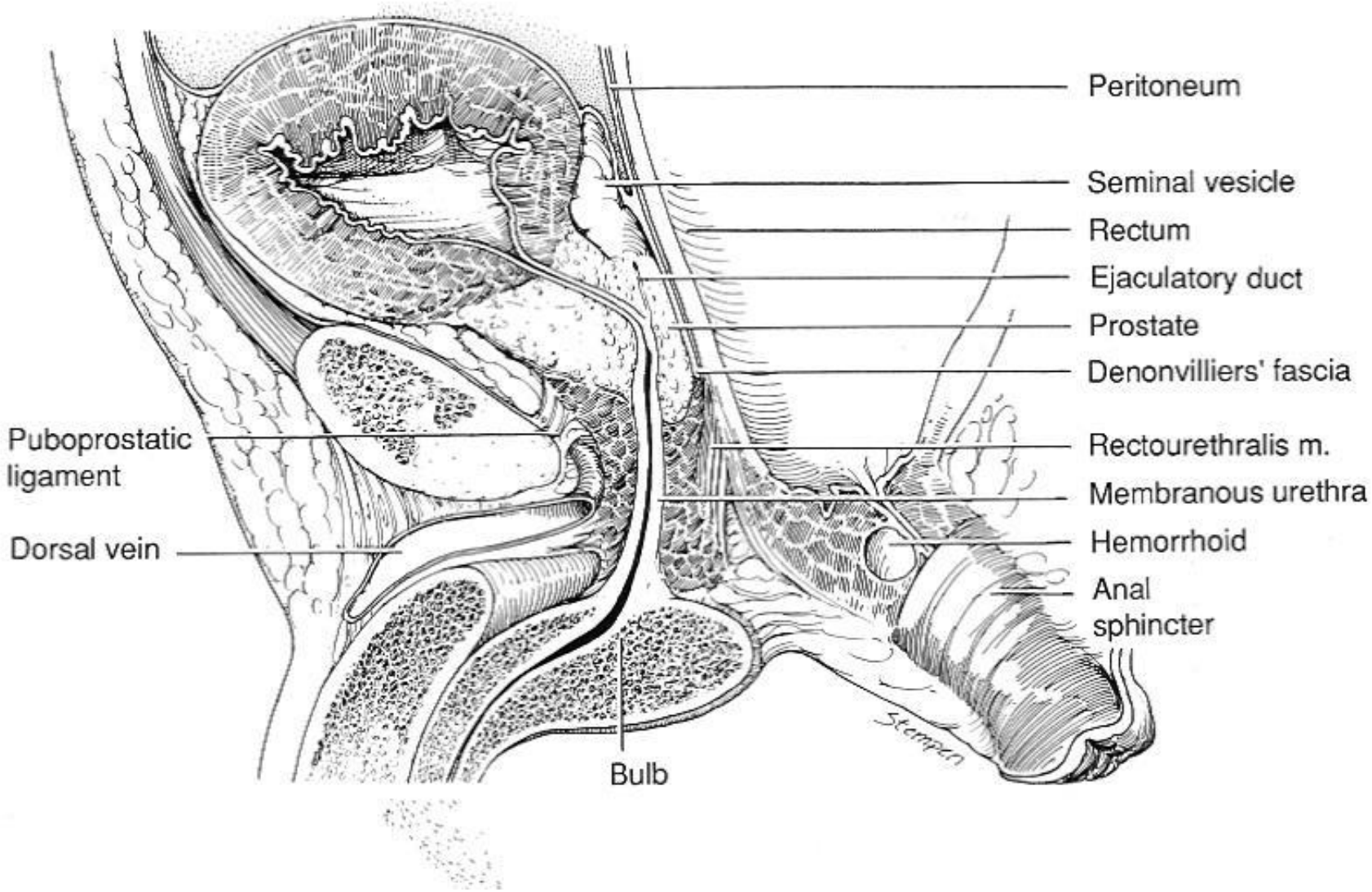
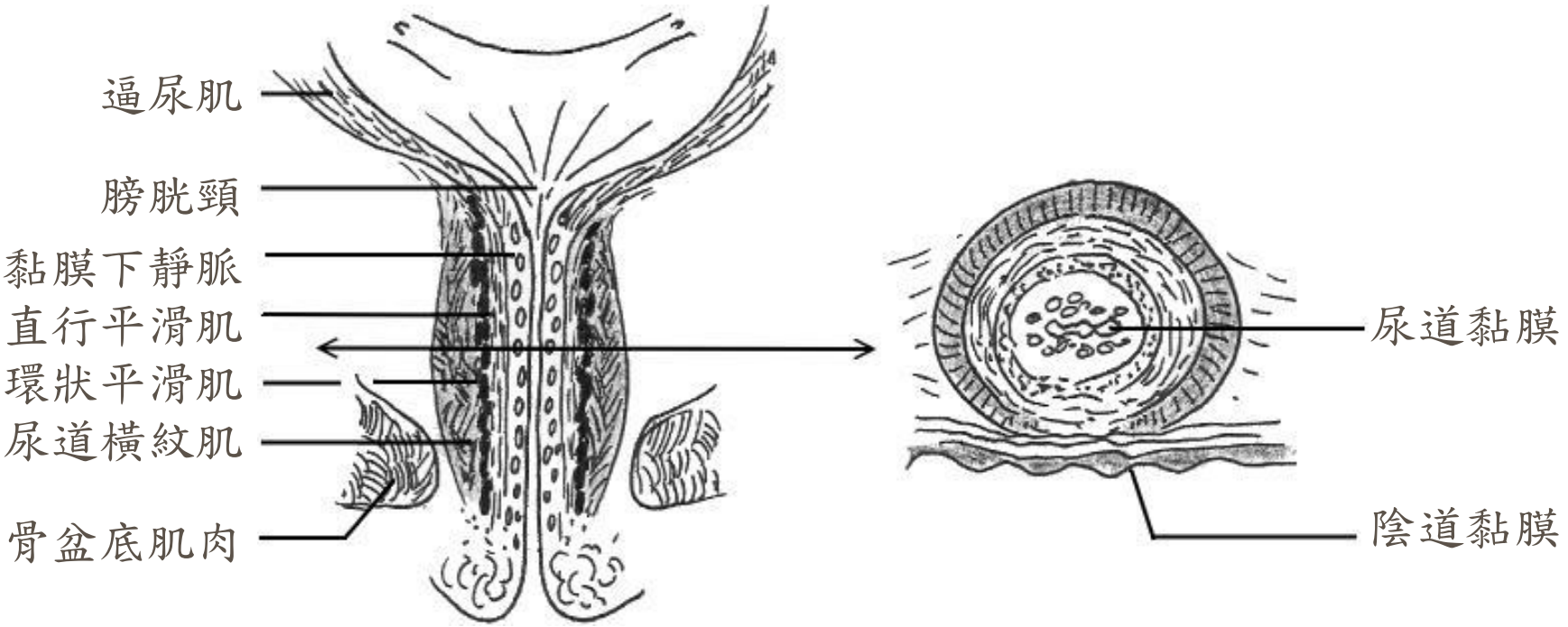
Lower Urinary Tract Function and Pharmacology

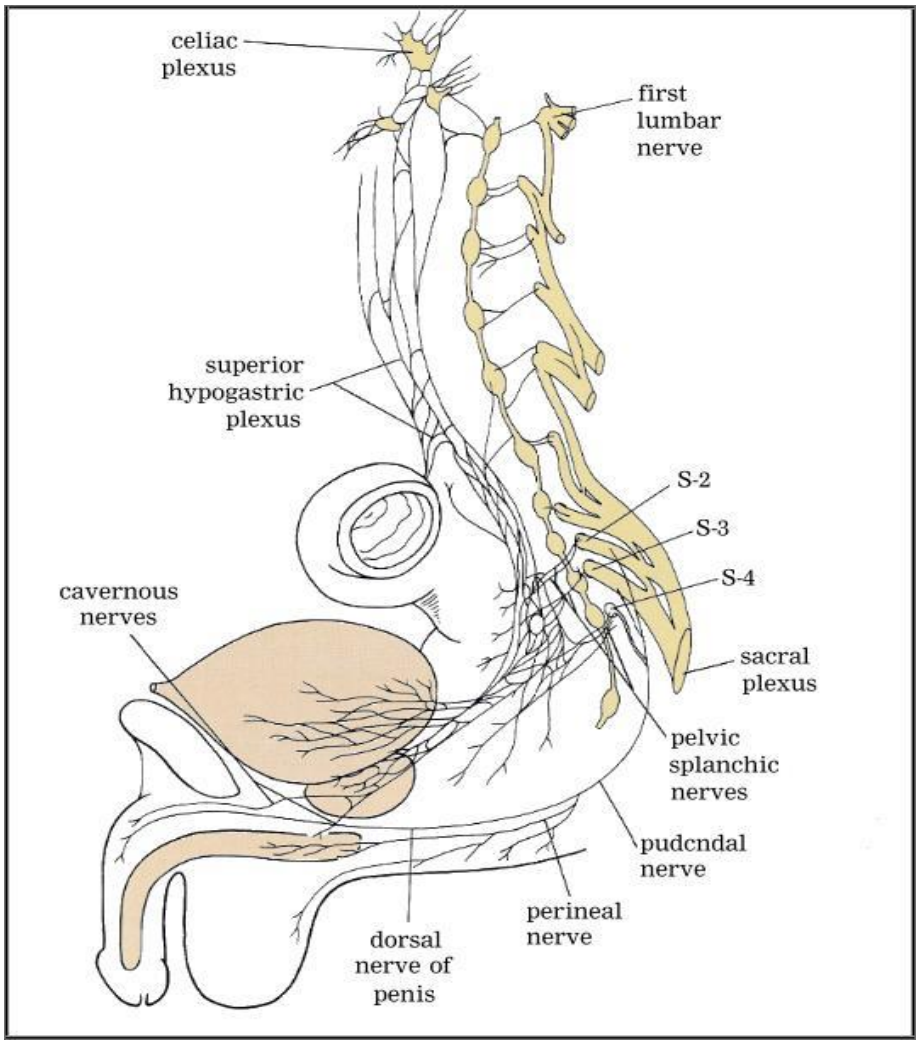
Anatomy of Male Urethra and Adjacent Organs



Anatomy of Urethra and External Urethral Sphincter

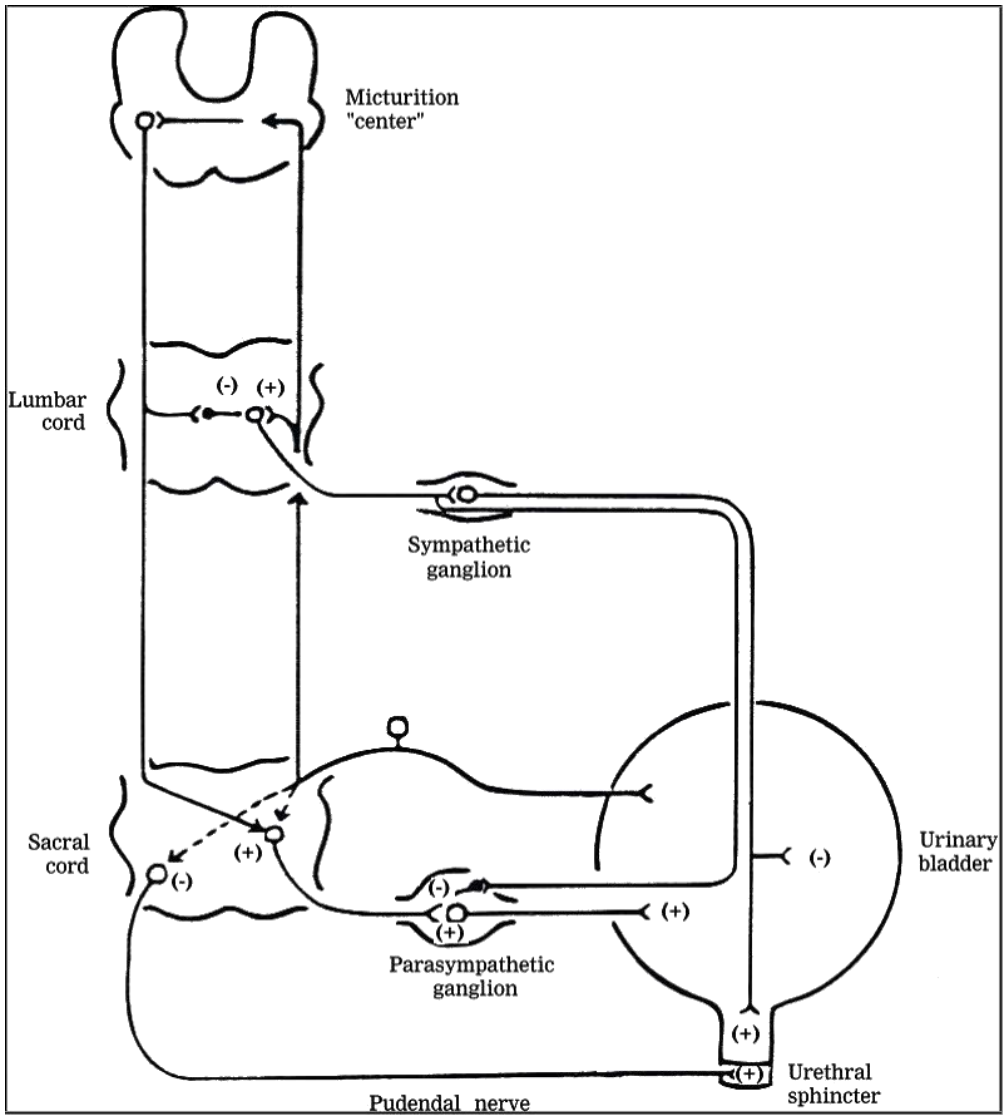


Neuroanatomy of Lower Urinary Tract



- Storage– Stability and good compliance of Bladder
- Empty – Contraction of detrusor and opening of Urethra
- Parasympathetic - Pelvic nerve
- Sympathetic - Hypogastric nerve
- Somatic nerves- Pudendal nerve

Neuroanatomy of Micturition



- Micturition reflex center – sacral cords 2-4
- Micturition control center – pons
- Sensory motor center – frontal lobe
- Limbic system
- Cerebellum, Basal ganglia

Innervation of Lower Urinary Tract

- Bladder
  - cholinergic parasympathetic: contraction
  - beta-adrenergic & NO: relaxation
- Bladder neck
  - alpha-adrenergic: contraction
- Urethral muscles
  - cholinergic parasympathetic, NO, cholinergic somatic nerves

- **In the human bladder, where the mRNAs for all the five pharmacologically defined receptors, M1 to M5, have been demonstrated**
- **The predominance of mRNAs encoding M2 and M3 receptors**
- **In human detrusor, the M3 receptors are believed to be the most important for contraction**

Storage dysfunction

- Bladder hypersensitivity
- Low bladder compliance
- Detrusor overactivity – neurogenic or idiopathic
- Low urethral resistance
- Bladder outlet obstruction
- Combination of the above

- Main pathways for muscarinic receptor activation of the detrusor via M3 receptors are Ca2+ influx and inhibition of myosin light-chain phosphatase through activation of Rho-kinase.
- The signaling mechanisms for the M2 receptors are less clear than those for M3
  - Generally, M1, M3, and M5 receptors are considered to couple preferentially to Gq/11, activating phosphoinositide hydrolysis, in turn leading to mobilization of intracellular calcium (Ca2+).
  - M2 and M4 receptors couple to pertussis toxin–sensitive Gi/o, resulting in inhibition of adenylate cyclase activity

Anticholinergics Treatment

- Act mainly during the storage phase, decreasing urgency and increasing bladder capacity
- Behavioral therapy should always be used in conjunction with drug therapy for OAB/DO because most studies show the effects of the two combined are greater than the effect of either alone
  - Oxybutynin – the most effective and safe drug currently available
  - Detrusitol, solifenacin – M3 antagonist, less salivary and GI side effects than Ditropan
  - Flavoxate – mild effect on detrusor
  - Imipramine – central and anticholinergics

Drugs Used in the Treatment of Detrusor Overactivity (ICI, 2008; Andersson et al, 2009)

ANTIMUSCARINIC DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Fesoterodine	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs Acting on Membrane Channels		
Calcium antagonists	2	D
Potassium channel openers	2	D
Drugs with Mixed Actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Duloxetin	2	C

Side effects of Anticholinergic

- Post-synaptic receptors M1 and M2 are widespread in CNS, anticholinergics may have cognitive dysfunction, especially in elderly
- Dry mouth, constipation, blurred vision
- Darifenacin has 11-fold higher affinity to M3 than M2 receptors and a 5-fold lower affinity for M receptors in parotid gland

β-Adrenergic Receptor Agonists

- **3 subtypes (β1, β2, and β3) have been identified in the detrusor**
- real-time polymerase chain reaction, have revealed a **predominant expression of β3-AR mRNA**
- Mechanism by which β-ARs induce detrusor relaxation
  - activation of adenylyl cyclase with the subsequent formation of cAMP through the action of the G-proteins
  - K+ channels
- Mirabegron is the first and only **β3 agonist** approved by US FDA in June 2012

Antidepressants

- **Tricyclic antidepressants three major pharmacologic actions:**
- (1) they have some central and peripheral antimuscarinic effects
- (2) they block the active transport system in the presynaptic nerve ending , reuptake of the released amine neurotransmitters norepinephrine and serotonin
- (3) sedatives, an action that occurs presumably on a central basis but is perhaps related to antihistaminic properties

Botulinum Neurotoxin (BoNT).

- BoNT is produced by *Clostridium botulinum. Of the 7 subtypes of BoNT, subtype A* (BoNT/A) is the most relevant clinically.
- Inhibitor of the release of acetylcholine and other transmitters at the neuromuscular junction of somatic nerves in striated muscle and of autonomic nerves in smooth muscle
- BoNT has been developed as a secondline treatment option for patients with NDO with urinary incontinence or OAB symptoms and who are able and willing to perform CIC.

Pharmacology of Micturition- Decrease outlet resistance

- Decrease bladder neck & urethral resistance
- Alpha-adrenergic blockers- phenoxybenzamine, prazosin, terazosin, tamsulosin, doxazosin,
- Nitric oxide donors
- Botulinum toxin
- Polysynaptic blocker – baclofen, diazepam

Medical Therapy for BPH

- Prostatic smooth muscle tension was mediated by alpha 1-adrenoreceptors
- Smooth muscle contractions contribute 40% of outflow obstruction
- Alpha 1- blockers can rapidly improve Qmax and relieve LUTS
- Phenoxybenzamine, terazosin, doxazosin have side effect of dizziness and hypotension

Prostatic specific alpha- adrenoreceptor

- Alpha 1A- AR subtype comprises 70% of all alpha-1 receptors
- Alpha 1A-AR agonist – tamslosin has 13 x more affinity to prostatic smooth muscle than urethral muscle , 10 x than vascular smooth muscle
- Side effects are still reported
- Long-acting (once daily) dose

Hormone based medical therapy

- 5-alpha-reductase catalyzes conversion of testosterone to dihydrotestosterone
- Inhibition of 5-alpha-reductase can arrest prostatic growth and relieve obstruction
- Finasteride can improve symptom score, Qmax, QOL score
- Effective especially in prostatic weight of >40 gm and effective in prostatic hematuria

Combination therapy with alpha-blocker and 5AR-i

- Terazosin is effective therapy, finasteride was not, combination was no more effective than terazosin alone (Lepor, N Engl J Med 1996; 335: 533)
- Combined dibenyline and finasteride has an additive effect than dibenyline or finasteride alone in improvement of Qmax and prostatic size*

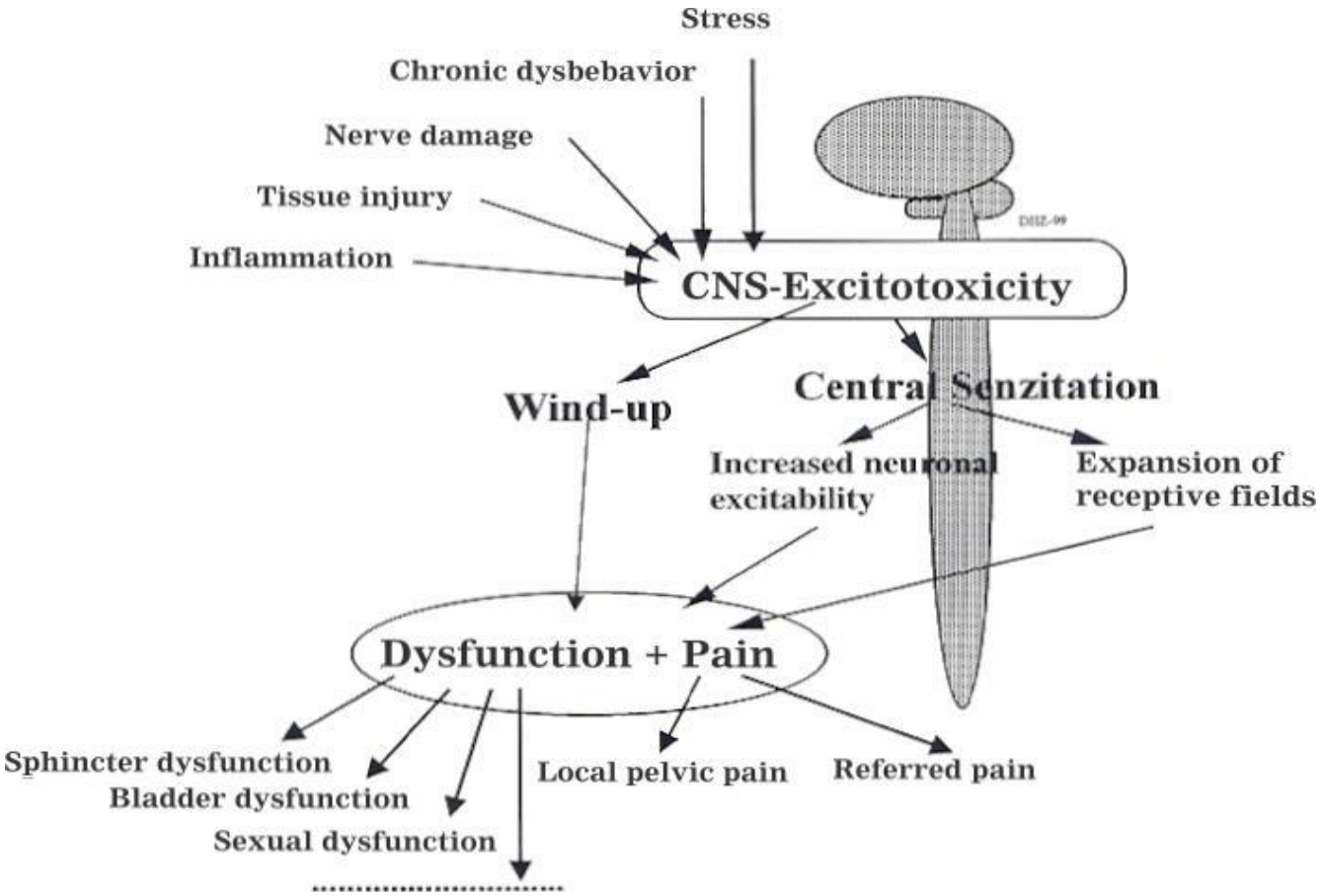
- Nitric Oxide : neurotransmitter capable of producing smooth muscle relaxation, at least in the female rabbit urethra, pig urethra, and human bladder neck
  - Sublingual administration of isosorbide dinitrate (10 mg) could significantly reduce the resting pressure of the external urethral sphincter for at least 1 hour
- May be a potential pharmacologic option to treat detrusor–striated sphincter dyssynergia in spinal cord–injured patients.

Detrusor overactivity

- Neurogenic detrusor hyperreflexia
- Detrusor instability related to bladder outlet obstruction
- Idiopathic detrusor instability
- ICS recommended Detrusor overactivity

  May be neurogenic, myogenic or idiopathic

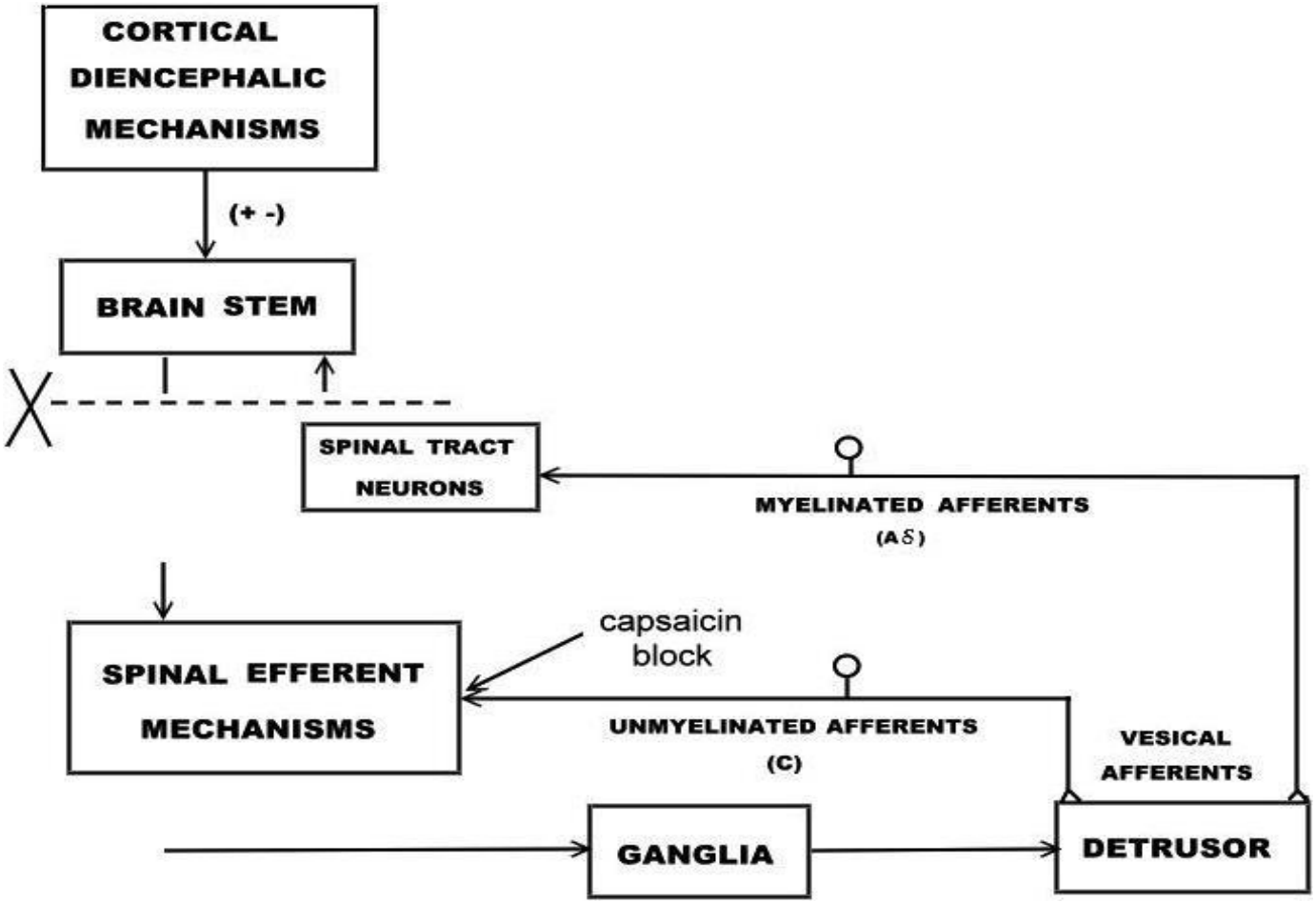
Neurobiological background of pelvic floor dysfunction



Sensory Afferents

- A-delta fibers – Micturition reflex, stretch and fullness sensation
- C-fibers – Noxious sensation, capsaicin sensitive primary afferents (CSPA)
- Dual sensory afferents in mammalian urinary bladder

Dual Sensory Innervation of Urinary Bladder



Micturition detrusor pressure- depends on urethral resistance

- High voiding pressure indicates a greater urethral resistance
- Low voiding pressure indicates a lower urethral resistance or a low detrusor contractility
- Efficient bladder empty depends on a sustained detrusor contraction

Pharmacology of Micturition- Increase empty efficiency

- Parasympathomimetic agent- Bethanechol (Urecholine)
- Adrenergic blockers- inhibition of detrusor relaxation (?)

Pharmacology of Micturition- Increase outlet resistance

- Increase smooth muscle tone
  - Imipramine, methylephedrine
- Increase striated muscle tone
  - Nitric oxide synthase inhibitor
  - Pelvic floor muscle training

Combination of Medication- Improve Voiding Efficiency

- Increased bladder sensation- intravesical capsaicin, RTX
- Detrusor overactivity- anticholinergic, intravesical RTX, botulinum toxin
- Detrusor underactivity – parasympathomimetics, alpha-blocker, NO donors, striated muscle relaxant, periurethral botulinum toxin injection

Combined Medication – Improved Voiding Efficiency

Urethral sphincter hypertonicity- alpha-blocker, NO donors, striated skeletal muscle relaxant

- Urethral sphincter overactivity- alpha-blocker, striated muscle relaxant, NO donors, botulinum toxin
- Bladder neck dysfunction- alpha-adrenergic blocker

Combined Medication- Improved Storage Efficiency

- Detrusor Overactivity- anticholinergics, sympathomimetics, imipramine
- Intrinsic sphincter deficiency- imipramine, sympathomimetics
- DHIC- depends on voiding efficiency and grades of incontinence