Medical Pharmacology

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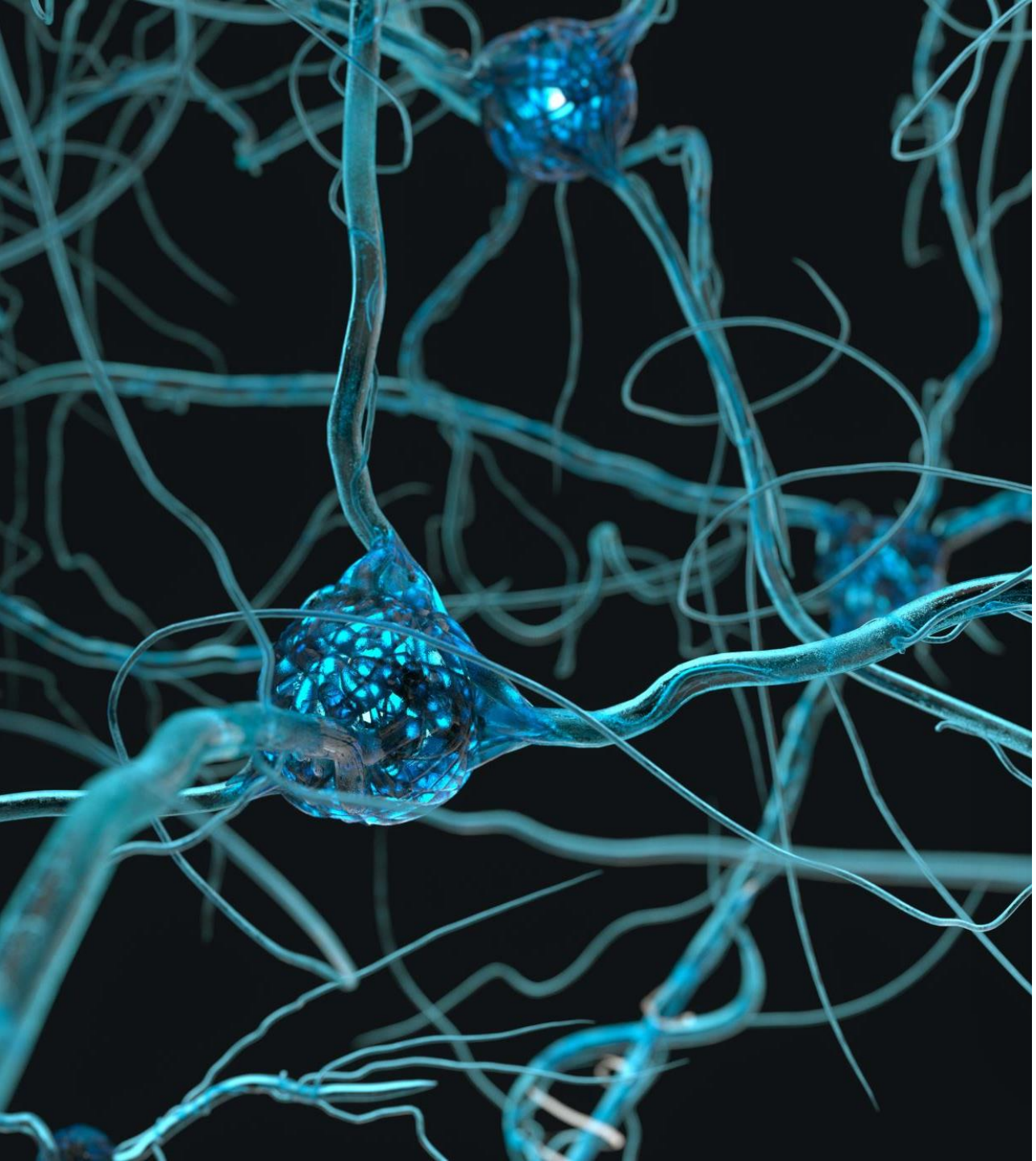
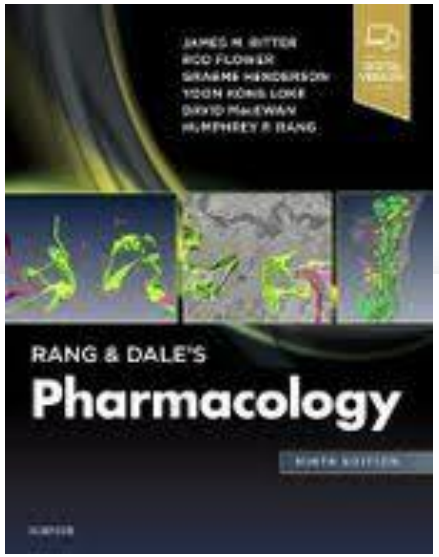
Celebrating 50 YEARS 1970 - 2020



Genitourinary Drugs



Rang & Dale's Pharmacology

10th ed 2020

Chap 29, 35

Genitourinary Drugs

THERAPEUTIC CLASS	SUB CLASS	EXEMPLAR
Drugs for sexual dysfunction	Phosphodiesterase 5 inhibitors	sildenafil
Drugs for urinary incontinence	Anticholinergics (genitourinary)	oxybutynin
	desmopressin	
Drugs for benign prostatic hyperplasia and prostatitis	Selective alpha-blockers (genitourinary)	tamsulosin
	5-Alpha-reductase inhibitors	dutasteride

Drugs for sexual dysfunction - PDE 5 inhibitors

Exemplar

- sildenafil, tadalafil and avanafil

Mechanism of action

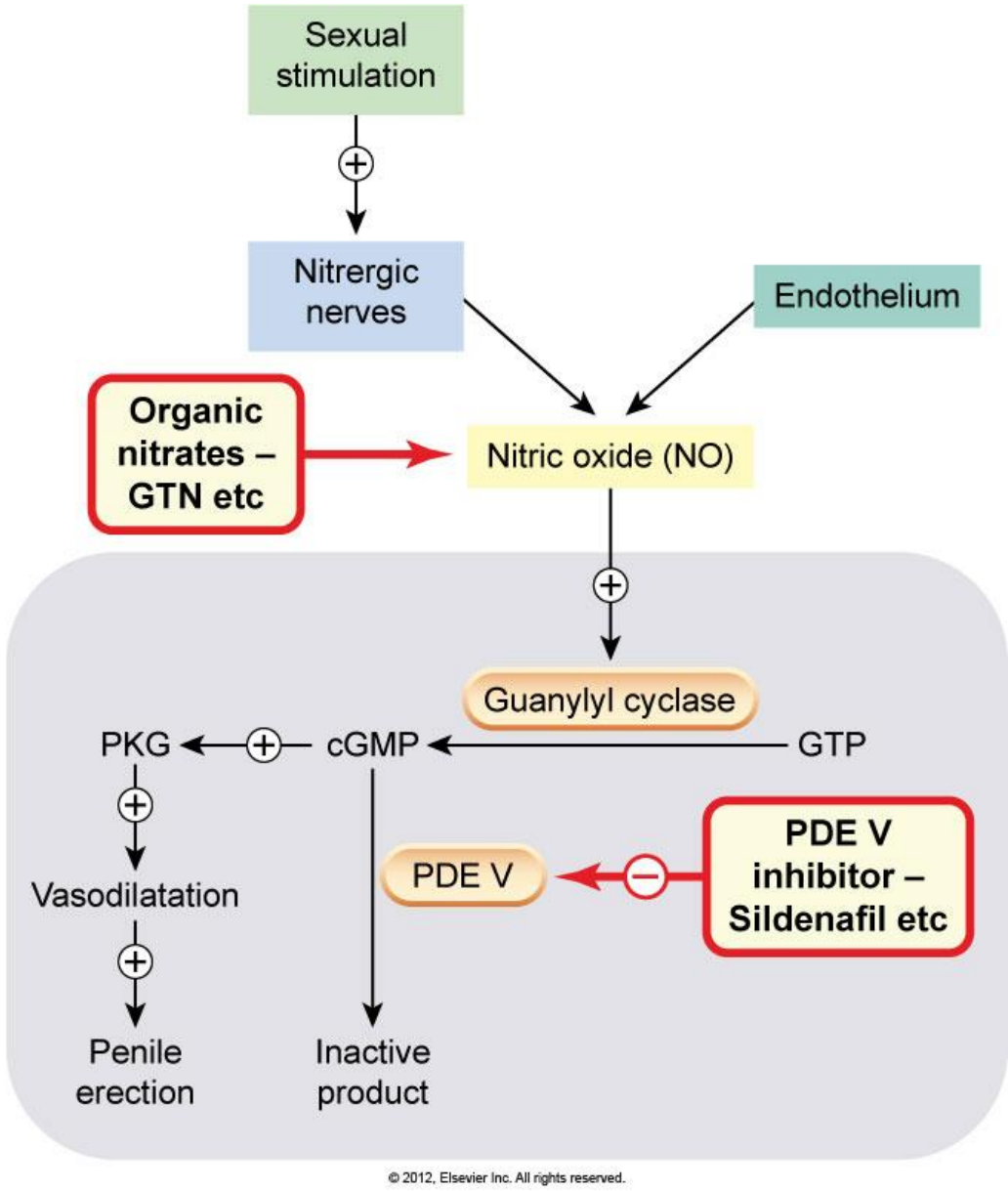
- penile erection results from dilation of the corpus cavernosa smooth muscle and increased blood flow
- dilation due to nitric oxide (NO), which stimulates soluble GC to synthesise cGMP, in turn activates PKG, leads to decreased cytosolic Ca2+ and smooth muscle relaxation
- Phosphodiesterase-5 normally breaks down cGMP

Adverse effects / Precautions

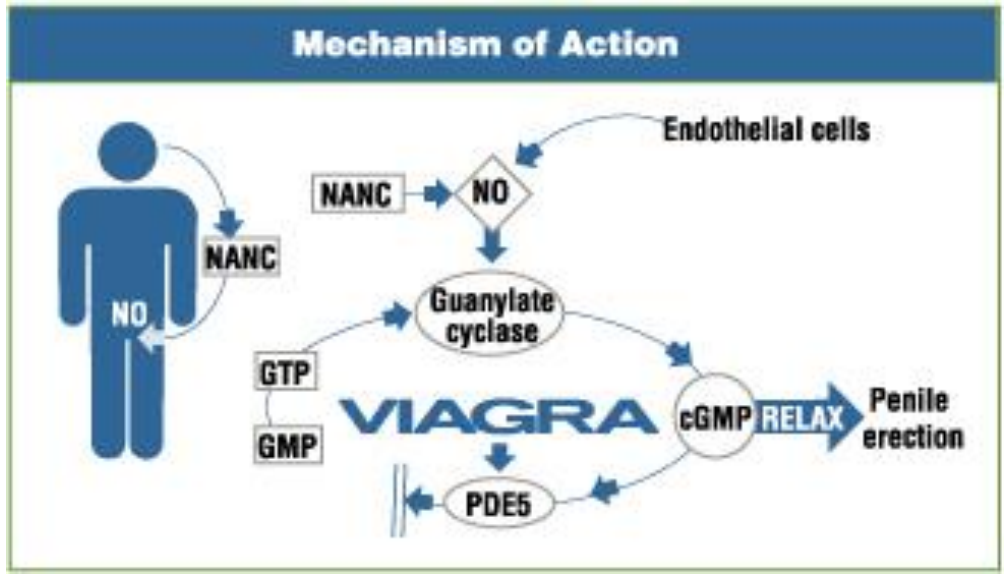
- headache, flushing, priapism, dizziness, vision loss due to non-arteritic anterior ischemic optic neuropathy (NAION)
- contraindicated with nitric oxide donors (nitrates)
- precautions in CV disease

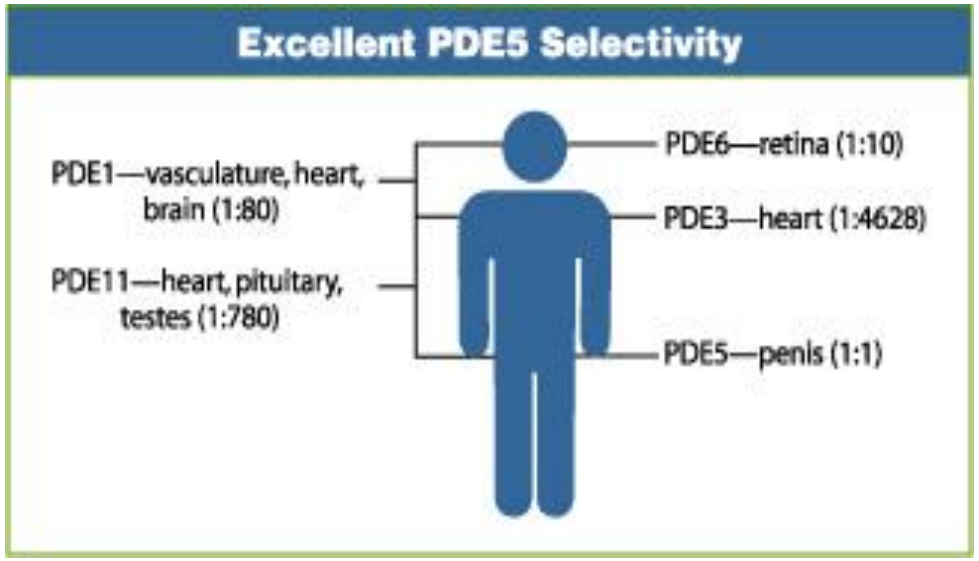
Drugs for sexual (erectile) dysfunction

- PDE 5 inhibitors



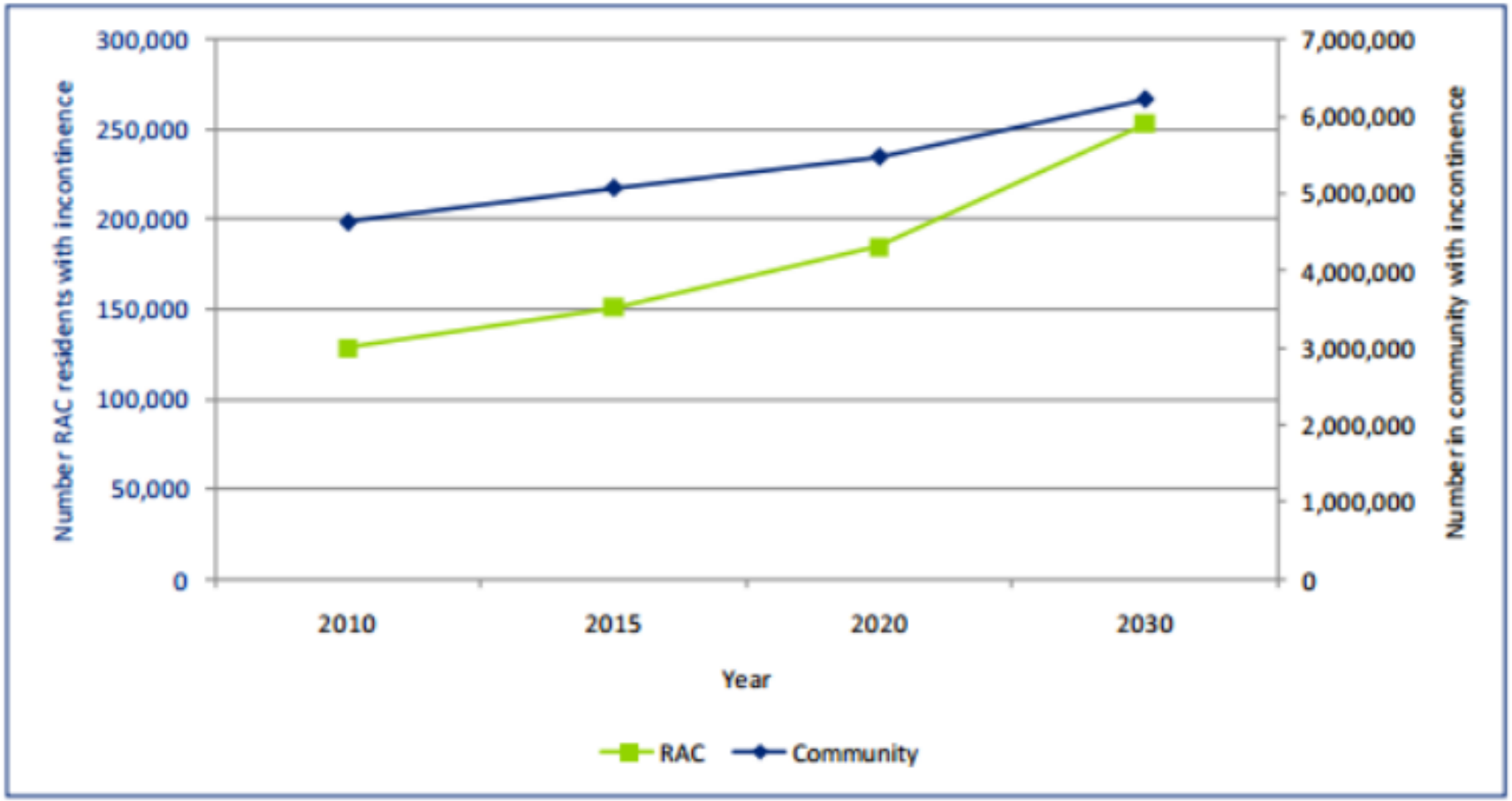
Drugs for sexual dysfunction - PDE 5 inhibitors





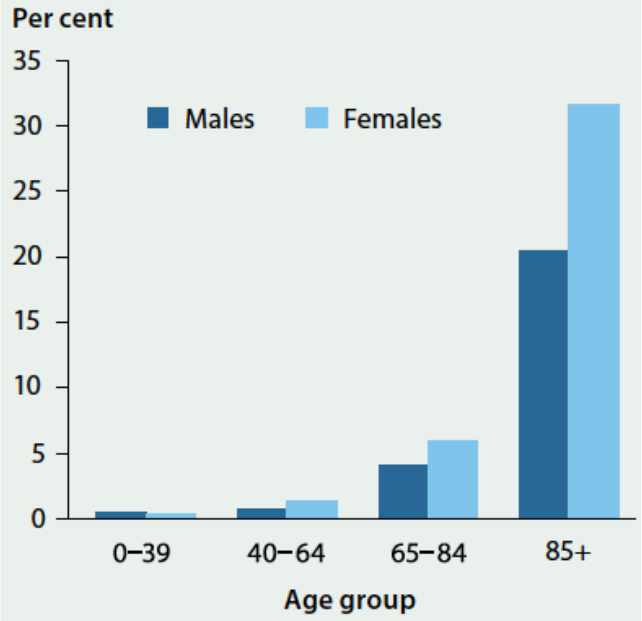
Urinary incontinence

Chart i: Projected prevalence of incontinence in Australians aged 15 years and over, 2010 to 2030



Source: Hawthorne (2006), Access Economics Demographic Model (AEDEM), Department of Health and Ageing, Ageing and aged care data warehouse[1], Productivity Commission (PC) (2010).

Figure 3.16.1: Prevalence of severe incontinence, by age and sex, 2012

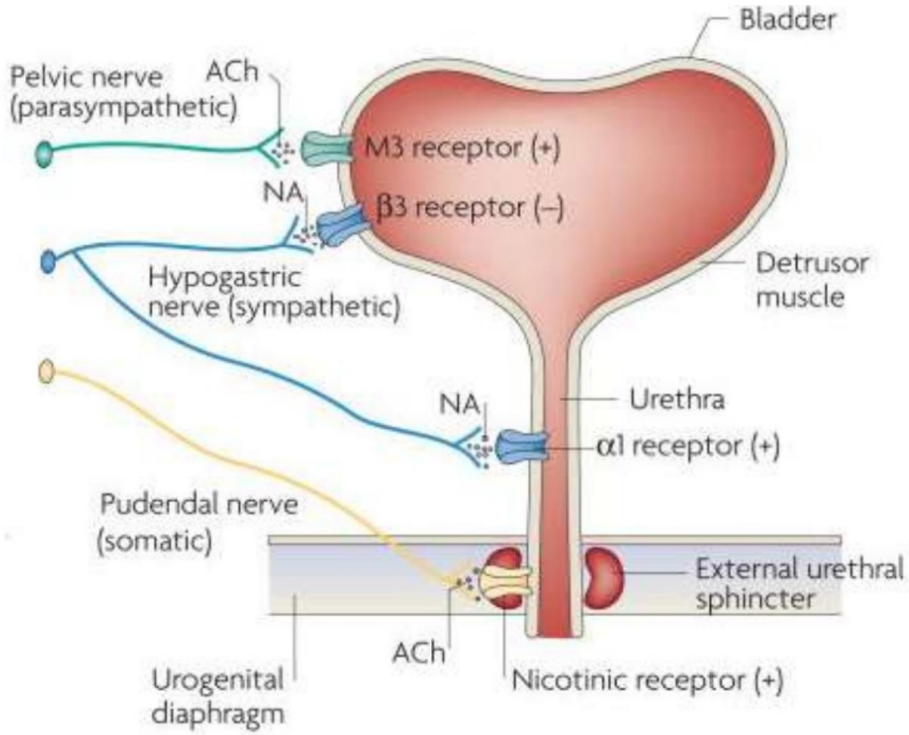


Source: AIHW analysis of the 2012 Survey of Disability, Ageing and Carers (ABS 2013).

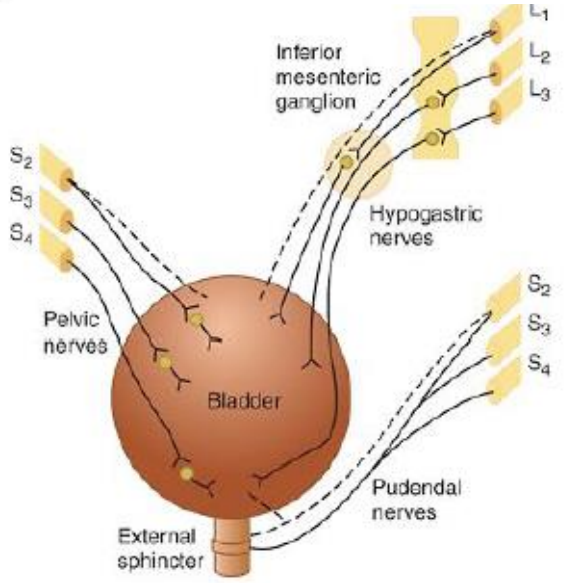
Bladder Nerves

HRM

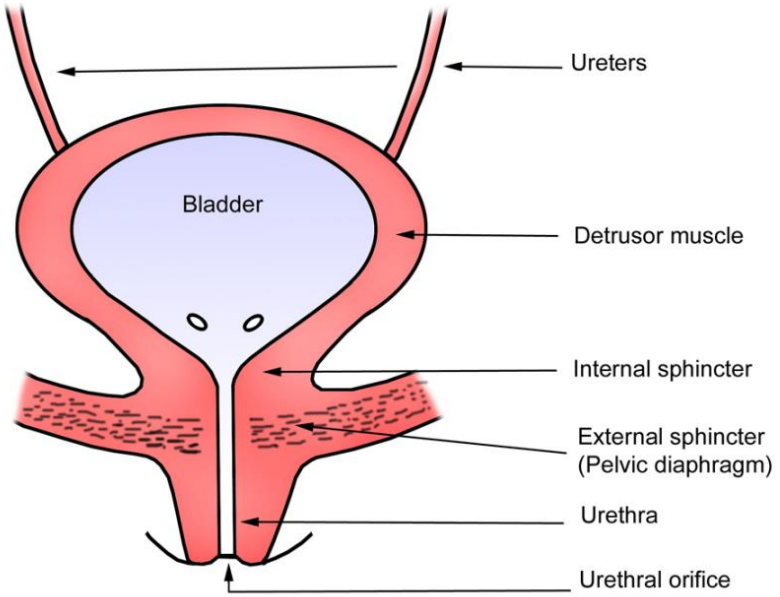
Somatic	• Pudendal Nerves (S2, S3, S4) • External urethral sphincter
Sympathetic	• Hypogastric Nerves (L1, L2, L3) • Bladder wall relaxation, internal sphincter contraction
Parasympathetic	• Pelvic Nerves (S2, S3, S4) • Bladder wall contraction, internal sphincter relaxation



- Parasympathetic Supply – Bladder detrusor muscle contraction and Internal sphincter relaxation
  - Facilitate emptying
- Sympathetic Nerves – Inhibition and relaxation of the detrusor – via β3 receptors; Contraction of internal sphincter – via α 1 receptor
  - Facilitate storage
- Somatic Nerves – Control the external sphincter – Nicotinic receptor



Drugs for urinary incontinence - Anticholinergics



Exemplar

- Oxybutynin, solifenacin

Indications

- overactive bladder, urge incontinence
  - symptoms include urgency, frequency, nocturia
  - caused by spontaneous detrusor contractions

Mechanism of action

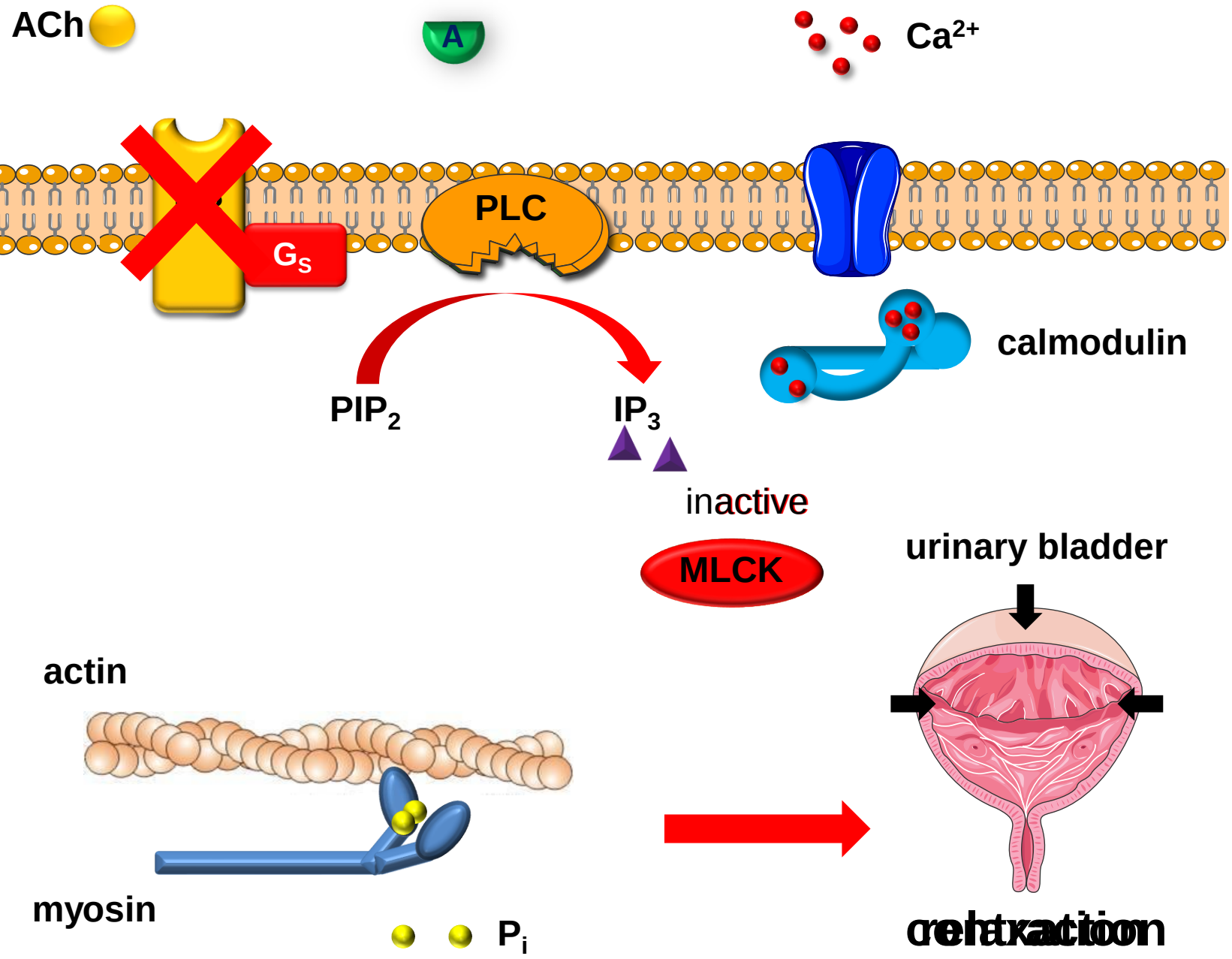
- selectively (?) inhibits M3 receptors on detrusor smooth muscle

Adverse effects / Precautions

- dry mouth, constipation, blurred vision
- contraindicated in glaucoma, caution in cognitive disorders, use with other anticholinergics

Anticholinergics

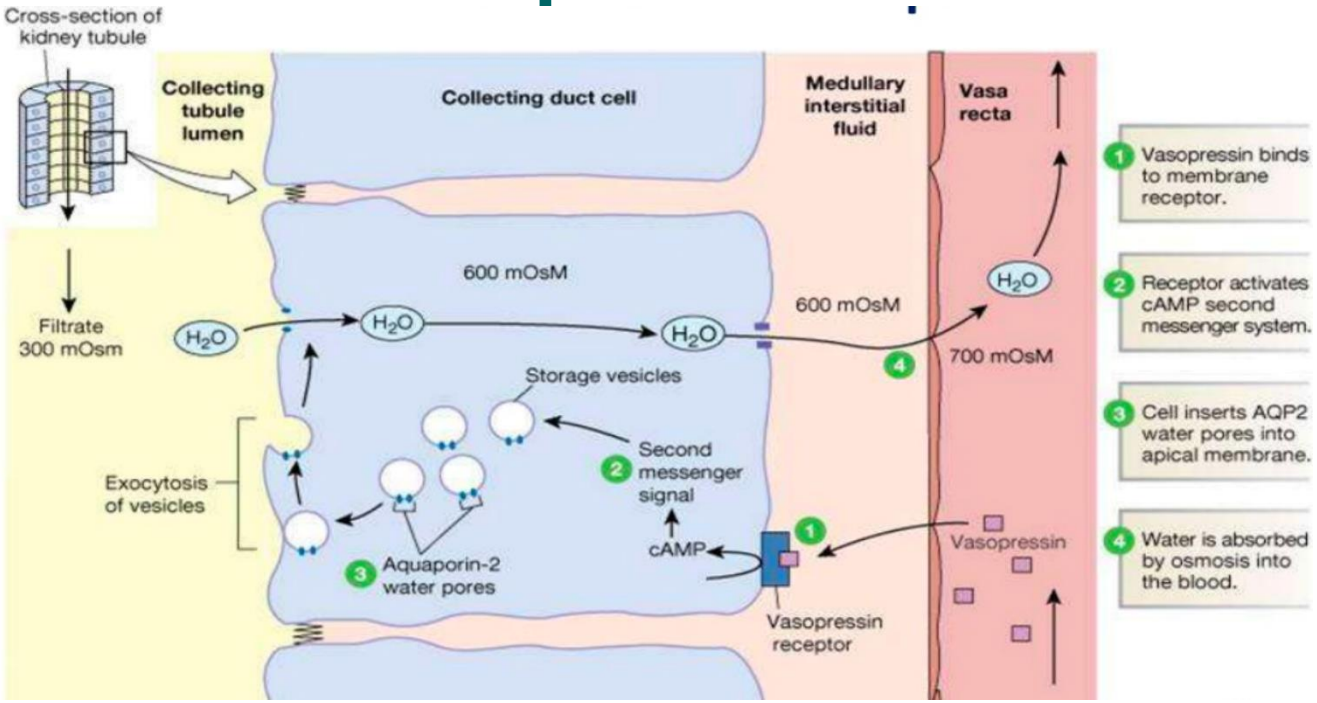
Genitourinary Drugs



Drugs for urinary incontinence - Desmopressin

Indications

- nocturnal enuresis in children
- nocturnal polyuria in adults
- also diabetes insipidus due to ADH deficiency



Mechanism of action

- ADH analogue
- acts at V2 (?) receptors in distal tubules and collecting ducts
- increases expression of aquaporins in the lumenal membrane thus increases water reuptake

Adverse effects / Precautions / other

- Hyponatraemia; contraindicated in HF, concurrent diuretic treatment
- Intranasal, oral, sublingual admin

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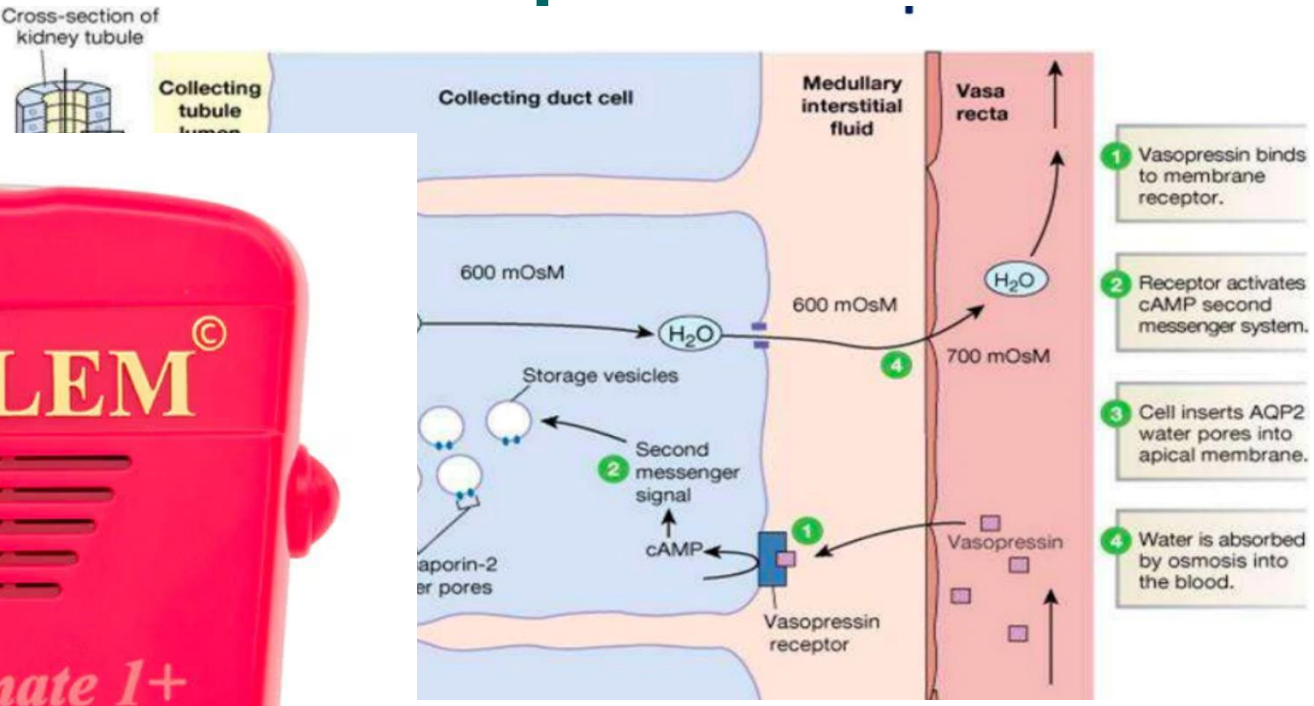

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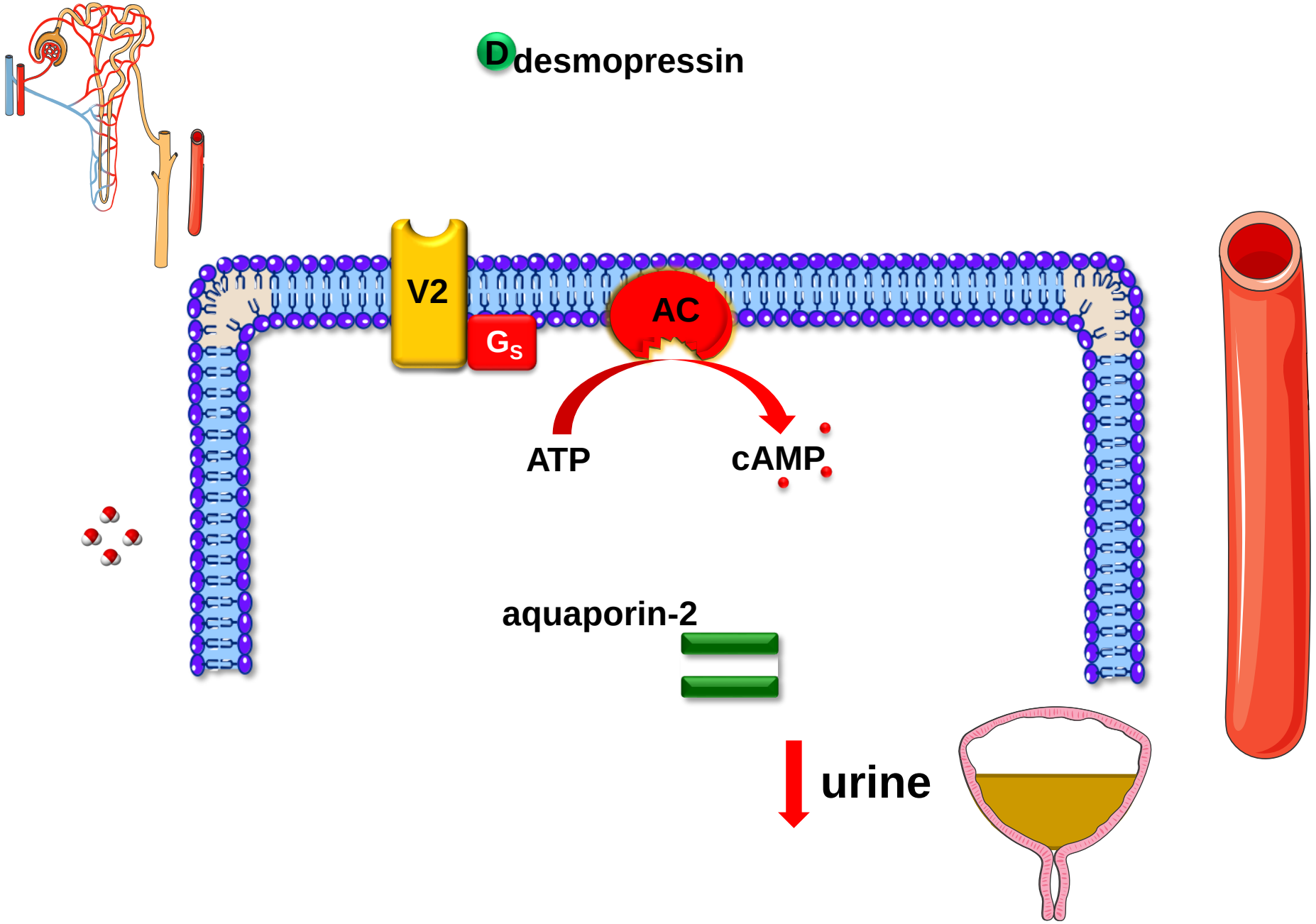
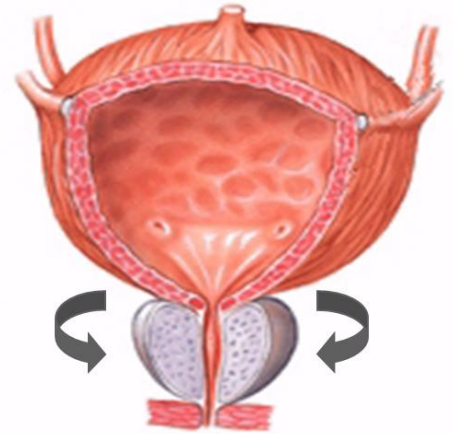
Desmopressin

Genitourinary Drugs



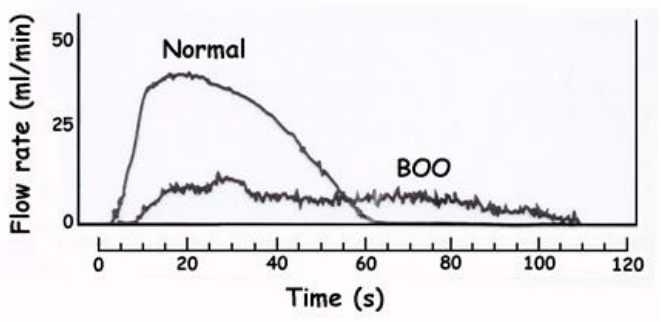
Bladder outlet obstruction (BOO)



- major cause benign prostatic hyperplasia (BPH)
- affects >90% males by 80y (40% symptomatic)

<u>BOO is due to :</u>

- compression by enlarged prostate
- contraction by bladder smooth muscle
- voiding & storage symptoms
- prostate hyperplasia mainly due to the dihydrotestosterone (DHT)

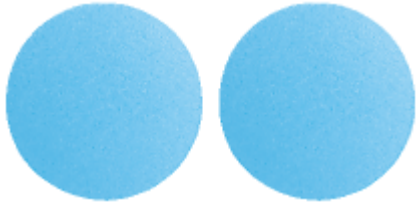


  - synthesised from testosterone by 5-alpha reductase
  - DHT forms complex with nuclear androgen receptors, which bind to DNA response elements to activate transcription, resulting in prostate cell growth and proliferation

Benign Prostatic Hyperplasia (BPH)

- Symptoms (Prostatism)
  - Weak urine stream prolonged voiding
  - Hesitancy in initiating voiding
  - A “stop and start” stream
  - Having to strain to urinate
  - Post-voiding dribbling
  - Sensation of incomplete emptying
  - Needing to urinate frequently
  - Feelings of urgency
  - Night-time urination
  - Overflow incontinence
  - Dysuria (painful urination)

Drugs for benign prostatic hyperplasia (BPH) – 5-alpha-reductase inhibitors



Exemplar

- dutasteride, finasteride

Mechanism of action

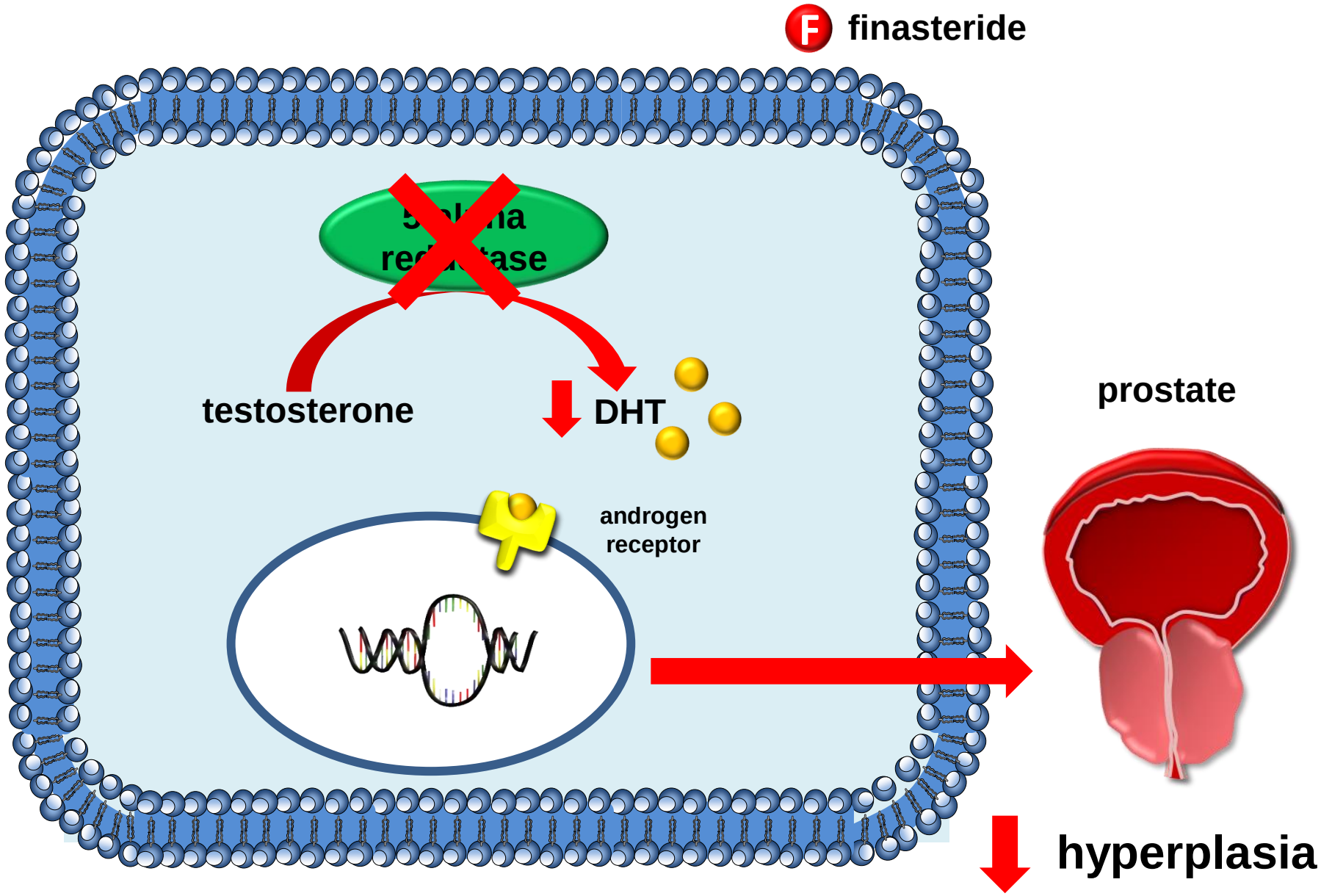
- 5-alpha-reductase inhibitors block conversion of testosterone to DHT, reducing hyperplasia and associated symptoms
- slow onset of action (months, compliance is important)

Adverse effects / Precautions

- reduced libido (5%), impotence (5%)
- breast tenderness
- contraindicated in those without a prostate

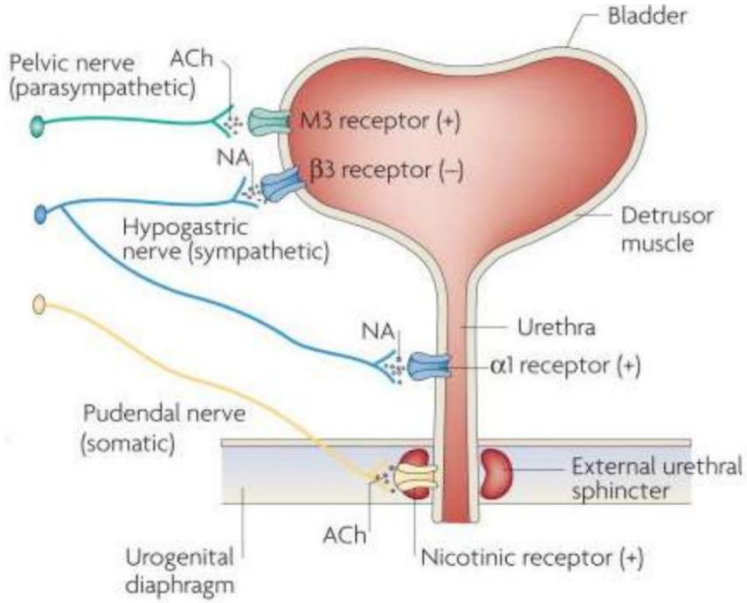
5-Alpha-reductase inhibitors

Genitourinary Drugs



Drugs for benign prostatic hyperplasia

- Selective alpha-blockers (genitourinary)



Exemplar

- Tamsulosin, silodosin, prazosin

Mechanism of action

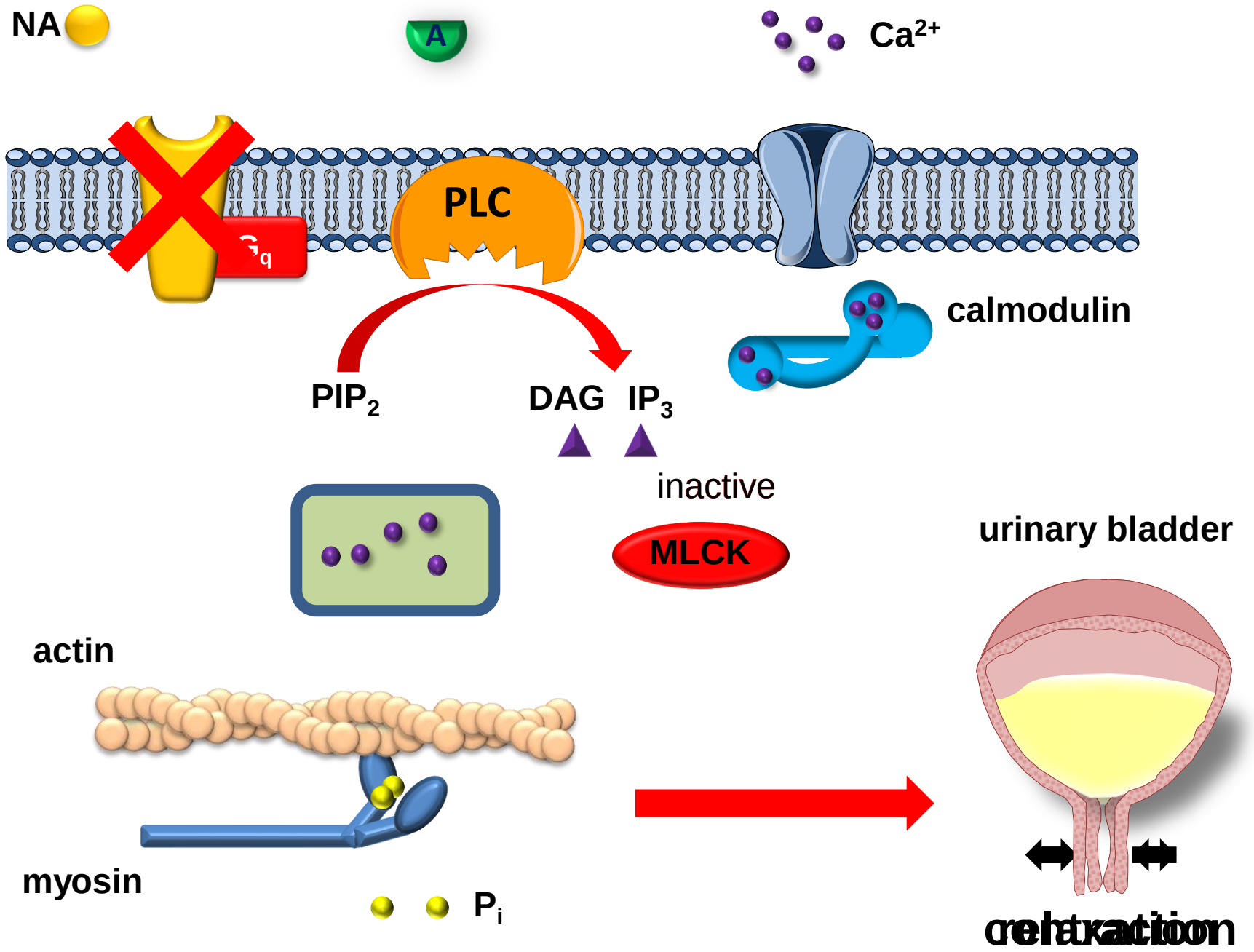
- Prostate and bladder neck smooth muscle tone is normally maintained by NE at alpha-1A adrenoceptors
- inhibition relaxes smooth muscle, improving urine flow; also inhibits prostate smooth muscle ~~hypertrophy~~ hyperplasia
- Tamsulosin is 10-fold selective for a1A-receptors compared with a1B

Adverse effects

- orthostatic hypotension, dizziness, retrograde ejaculation, impotence

Selective α-blockers (genitourinary)

Genitourinary Drugs



Review > Eur J Pharmacol. 2019 Jul 15;855:305-320. doi: 10.1016/j.ejphar.2019.04.047.
Epub 2019 May 5.

The pharmacology of α_1-adrenoceptor subtypes

James R Docherty [1]

Affiliations + expand

PMID: 31067439 DOI: 10.1016/j.ejphar.2019.04.047

Abstract

This review examines the functions of α_1-adrenoceptor subtypes, particularly in terms of contraction of smooth muscle. There are 3 subtypes of α_1-adrenoceptor, α_{1A}- α_{1B}- and α_{1D}-adrenoceptors. Evidence is presented that the postulated α_{1L}-adrenoceptor is simply the native α_{1A}-adrenoceptor at which prazosin has low potency. In most isolated tissue studies, smooth muscle contractions to exogenous agonists are mediated particularly by α_{1A}-, with a lesser role for α_{1D}-adrenoceptors, but α_{1B}-adrenoceptors are clearly involved in contractions of some tissues, for example, the spleen. However, nerve-evoked responses are the most crucial physiologically, so that these studies of exogenous agonists may overestimate the importance of α_{1A}-adrenoceptors. The major α_1-adrenoceptors involved in blood pressure control by sympathetic nerves are the α_{1D}- and the α_{1A}-adrenoceptors, mediating peripheral vasoconstrictor actions. As noradrenaline has high potency at α_{1D}-adrenceptors, these receptors mediate the fastest response and seem to be targets for neurally released noradrenaline especially to low frequency stimulation, with α_{1A}-adrenoceptors being more important at high frequencies of stimulation. This is true in rodent vas deferens and may be true in vasopressor nerves controlling peripheral resistance and tissue blood flow. The α_{IA}-adrenoceptor may act mainly through Ca^{2+} entry through L-type channels, whereas the α_{1D}-adrenoceptor may act mainly through T-type channels and exhaustable Ca^{2+} stores. α_1-Adrenoceptors may also act through non-G-protein linked second messenger systems. In many tissues, multiple subtypes of α-adrenoceptor are present, and this may be regarded as the norm rather than exception, although one receptor subtype is usually predominant.