PHARMACOLOGY

Male Reproduction

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DISCLOSURE

None

Use Statement

LEARNING OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing benign prostatic hyperplasia, hormone replacement needs, and erectile dysfunction
2. Explain the mechanism of action of drug classes for managing benign prostatic hyperplasia, hormone deficiencies, and erectile dysfunction and correlate with underlying pathophysiology
3. Describe adverse effects and contraindications to drug classes for managing benign prostatic hyperplasia, hormone deficiency, and erectile dysfunction
4. Describe the clinically important drug interactions of each drug class for managing benign prostatic hyperplasia, hormone deficiencies, and erectile dysfunction

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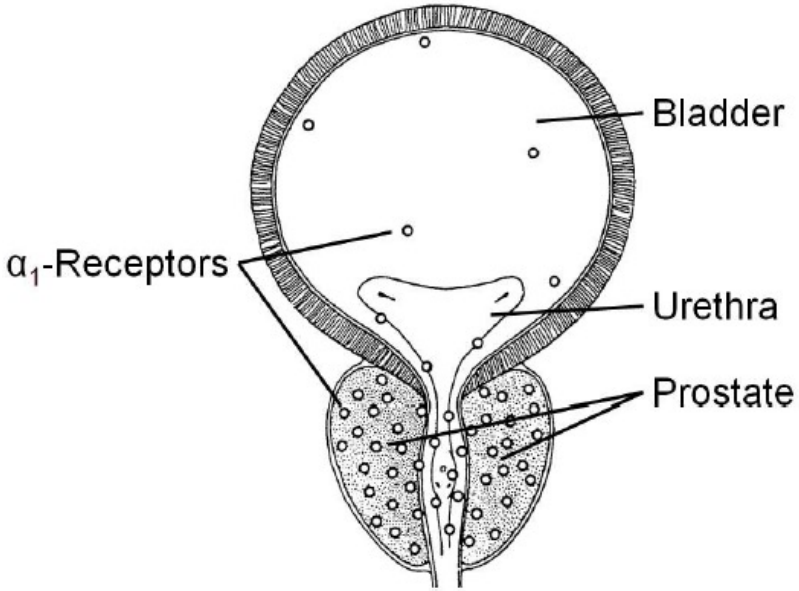
INTRODUCTION & PATHOPHYSIOLOGY REVIEW

PROSTATE

1. Epithelial tissue
   - Produces secretions
   - Under androgen control
2. Stromal tissue
   - Embedded with α1-adrenergic receptors (ARs) – stimulation → contraction → compression of urethra, ↓ urinary bladder emptying
3. Capsule
   - Fibrous connective tissue and smooth muscle
   - Embedded with α1-ARs (stimulation → contraction around urethra)



PROSTATE HORMONAL REGULATION

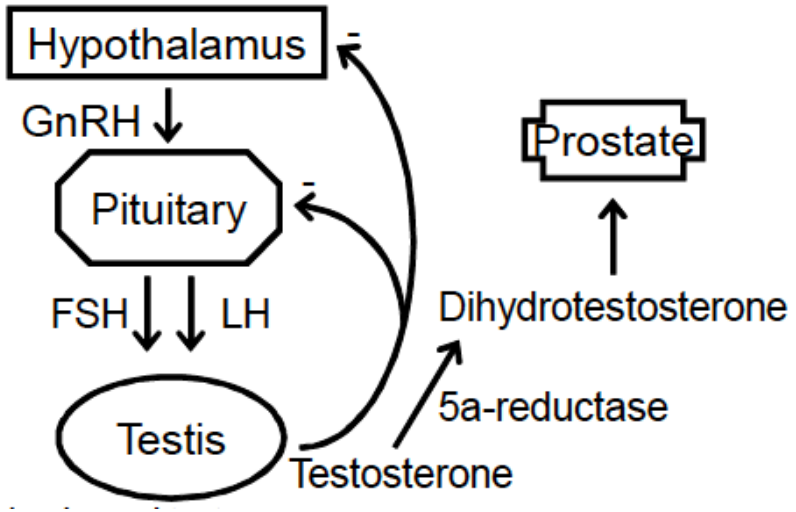
Normal growth/differentiation of prostate depends on presence of androgens, specifically dihydrotestosterone (DHT)

Testosterone is major androgenic hormone (testes primary source)

Testosterone or androgen precursors penetrate the prostatic cell by passive diffusion → converted to DHT by 5α-reductase

DHT exerts physiological effects by binding with a specific cytoplasmic receptor

- DHT-receptor complex transported to cell nucleus
- Transcription and ultimately translation of stored genetic material occur



BENIGN PROSTATIC HYPERPLASIA (BPH) PATHOGENESIS

Static

Anatomic enlargement of the prostate gland → physical block at the bladder neck → urinary outflow obstruction

Enlargement of the gland depends on androgen stimulation of epithelial tissue and estrogen stimulation of stromal tissue in the prostate

Dynamic

Relate to excessive α-adrenergic tone of the stromal component of prostate gland, bladder neck, and posterior urethra → contraction of prostate gland around urethra → narrowing of the urethral lumen

BPH PATHOGENESIS

Static Components

Production of new epithelial glands in the prostate and loss of programmed cell death, potentially due to androgens and chronic inflammation

Dynamic Components

Increased smooth muscle tone and resistance via alpha-adrenergic receptors

Prostate enlargement and anatomical obstruction of the urethra

Impacts bladder detrusor muscle activity
Increased detrusor muscle excitability and instability

Lower urinary tract symptoms (LUTS)

ACTIVE LEARNING

Based on what you know about the prostate, prostate hormonal regulation, and the pathogenesis of BPH, what do you hypothesize are potential drug targets for treatment of the static component of BPH? The dynamic component?

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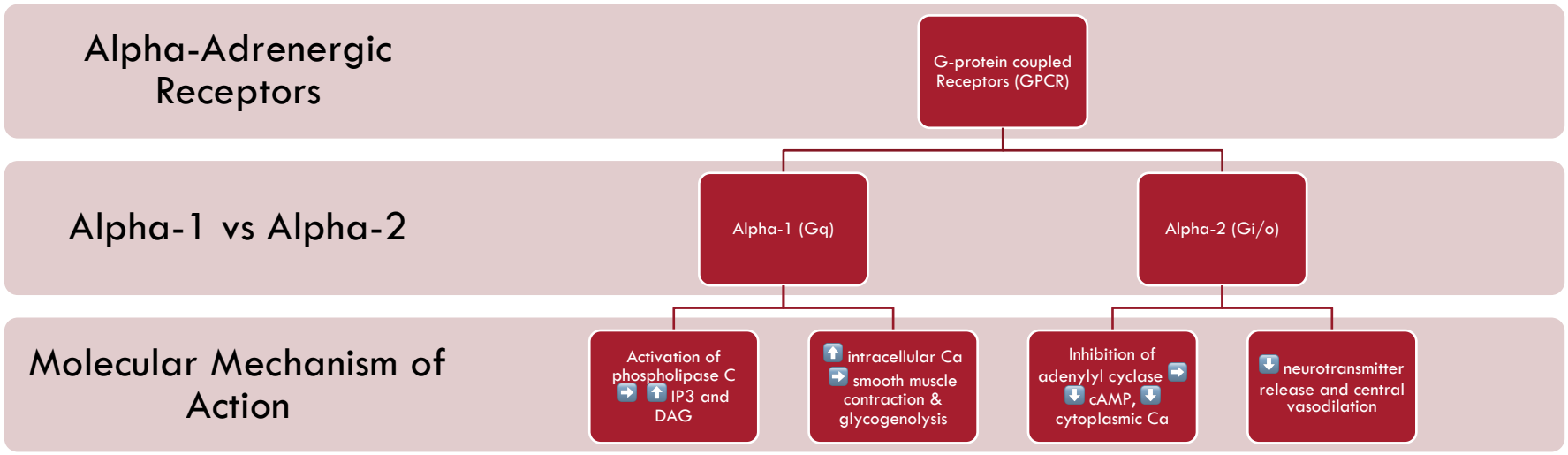
DRUGS FOR THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

ACTIVE LEARNING

Write down everything you remember about alpha-1 adrenergic receptors in 30 seconds.

ALPHA-ADRENERGIC RECEPTOR REFRESHER



ACTIVE LEARNING

Complete the missing information from the following table. You have 2 minutes to complete this individually or with partners.

Receptor Subtype	Stimulated By	Molecular Mechanism	Major Functions (where receptors located, effects; include locations/functions related to BPH)
Alpha-1			
Alpha-2			

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ALPHA-ADRENERGIC RECEPTOR ANTAGONISTS OR "ALPHA BLOCKERS"

ACTIVE LEARNING

In general, how would AGONIZING alpha-adrenergic receptors impact symptoms associated with BPH? How would ANTAGONIZING alpha-adrenergic receptors impact symptoms associated with BPH?

ALPHA-ADRENERGIC RECEPTOR ANTAGONISTS MOA

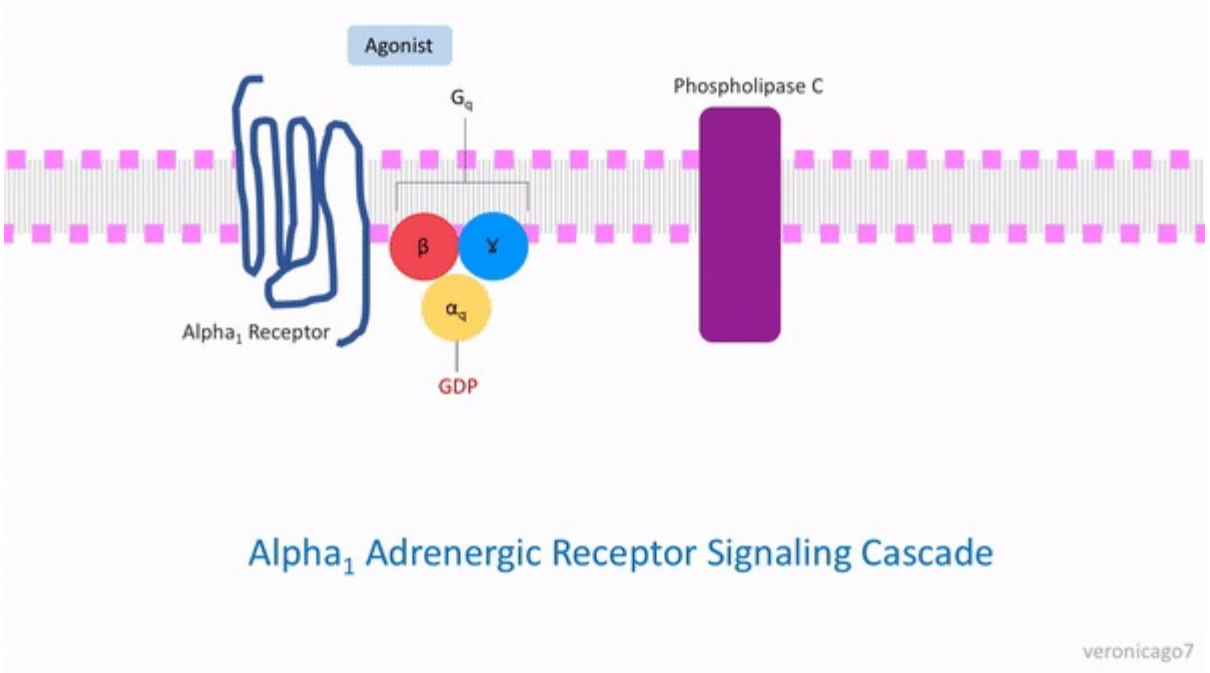


Image credit: https://en.wikipedia.org/wiki/Alpha_blocker

ACTIVE LEARNING

Do you think a selective or non-selective medication would be preferable for treating BPH? Explain your choice.

ALPHA-ADRENERGIC RECEPTOR ANTAGONISTS MOA

Block α1-adrenergic receptors in the prostate and bladder neck → relaxation of smooth muscle → widening of the urethral lumen → increased urinary flow

Some more selective for α1A-adrenergic receptor subtype

- Predominant subtype of α1-adrenergic receptor in the prostate

SELECTED SELECTIVE ALPHA BLOCKERS *-OSIN*

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Alfuzosin (Uroxatral) ▪ alpha1a-selective	Concurrent use with CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, ritonavir)	Hypotension (orthostatic) Dizziness Rhinitis Headache Anejaculation Priapism **Intraoperative floppy iris syndrome (IFIS)**	Anti-hypertensives Vasodilators Beta-blockers PDE-5 inhibitors
Doxazosin (Cardura) ▪ Non-selective	Hypersensitivity		
Silodosin (Rapaflo) ▪ Alpha1a-selective	Concurrent use with CYP3A4 inhibitors		
Tamsulosin (Contiflo, Flomaxtra) ▪ Aalpha1a-selective	Concurrent use with CYP3A4 inhibitors		
Terazosin (Hytrin) ▪ Non-selective	Hypersensitivity		

CLINICAL USE & ADME

Hypertension

Heart failure

Benign prostatic hyperplasia

Many are CYP3A4 substrates; avoid concurrent use with CYP3A4 inhibitors

ACTIVE LEARNING

What is the role of 5-alpha reductase in testosterone production?

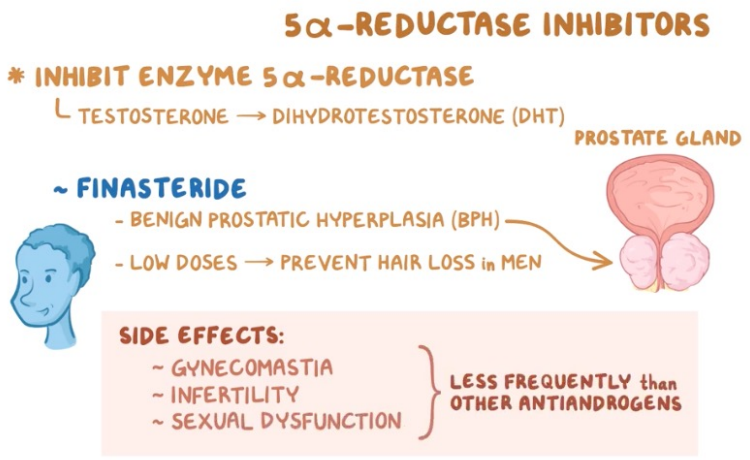
ACTIVE LEARNING

How might inhibiting 5-alpha reductase impact the static components of BPH?

5 ALPHA-REDUCTASE INHIBITORS MOA

5 alpha-reductase inhibitors prevent conversion of testosterone to (the more active) dihydrotestosterone (DHT) → ↓ tissue levels of DHT and ↓ prostate gland size

Treats the **static** component of urethral obstruction



SELECTED 5 ALPHA-REDUCTASE INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Dutasteride (Avodart)	Concurrent use with potent CYP3A4 inhibitors	Gynecomastia Infertility Sexual dysfunction **Impacts fetal development**	Potent CYP3A4 inhibitors may increase dutasteride levels
Finasteride (Proscar)			
	CI: Pregnancy Cautions: Hepatic Impairment		

CLINICAL USE & ADME

BPH

Finasteride also used for hair loss

Dutasteride is a CYP3A4 substrates; avoid concurrent use with CYP3A4 inhibitors

SAW PALMETTO

Purported to
- Inhibit 5 alpha-reductase, COX-1 and COX-2, lipoxygenase
- Antagonize α1-adrenergic receptors and androgen receptors

Contraindications & cautions
- Patients taking anticoagulants or hormone therapy

Adverse effects
- GI disturbances (diarrhea or constipation, nausea) occur

Drug interactions
- Prolongs bleeding time (can ↑ effect of anticoagulants such as warfarin)
- Exhibits antiandrogen and antiestrogenic activity (avoid use with with any hormone therapy)

ACTIVE LEARNING

How might exogenous testosterone use impact:

- Prostate size

- BPH symptoms

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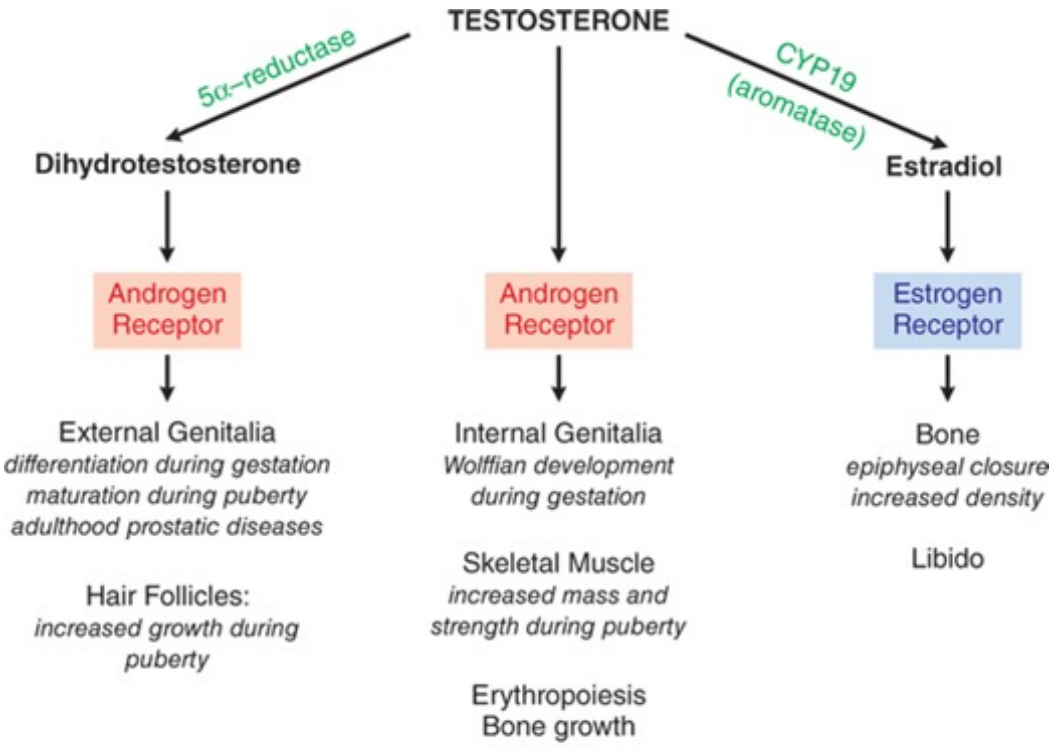
DRUGS FOR ANDROGEN DEFICIENCY

ANDROGEN MOA

- Testosterone works via
  1. Directly binding the AR
  2. Acting in tissues that express 5-alpha reductase
     - Via testosterone conversion to DHT (more active) → binds AR with higher affinity
  3. Acting as an estrogen

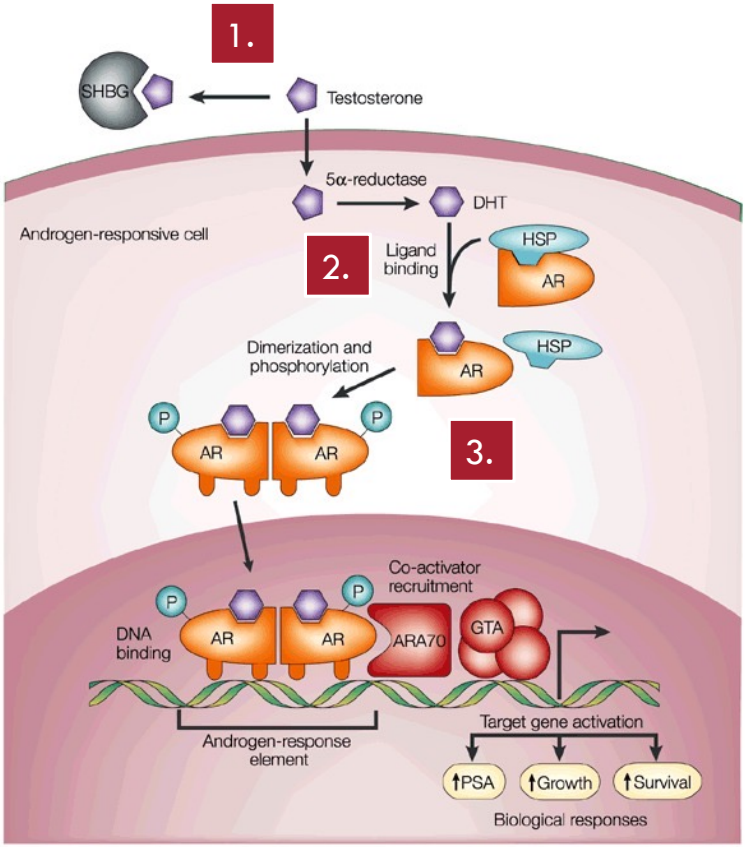


Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

ANDROGEN RECEPTOR (AR)

Ligand-dependent nuclear transcription factor; Member of the steroid hormone nuclear receptor family

1. Testosterone circulates bound to albumin and sex-hormone-binding globulin (SHBG)
2. Free testosterone enters prostate cells → converted to DHT via 5 alpha-reductase
3. DHT binds to cytosolic AR, causing release of stabilizing proteins and receptor phosphorylation



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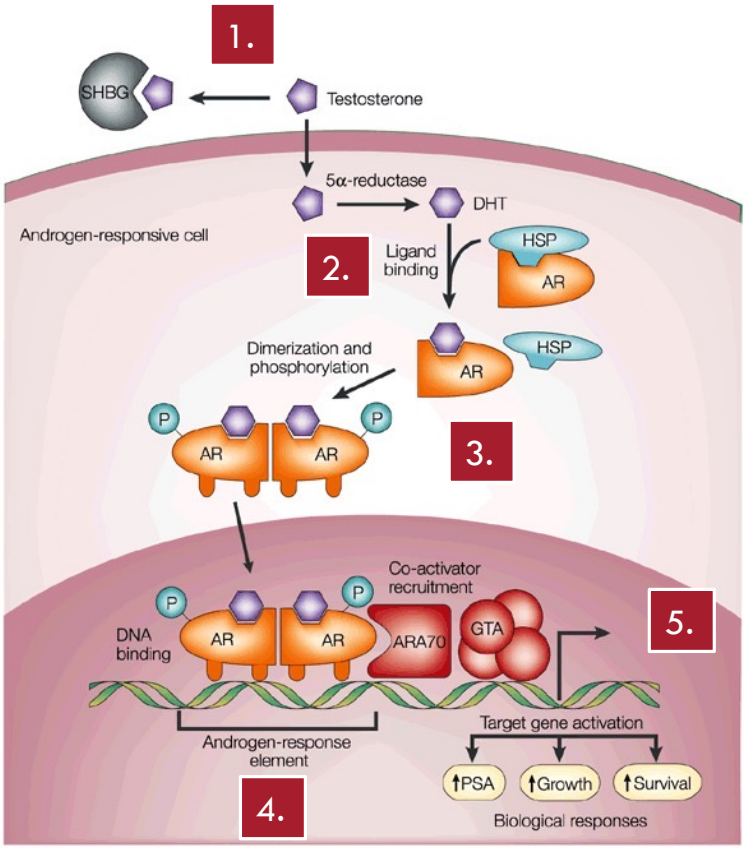
ANDROGEN RECEPTOR (AR)

4. AR-DHT complex translocates to the nucleus and binds androgen-response element (ARE) of target genes
5. Activation or repression of target genes leads to biological responses



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SELECTED THERAPEUTIC ANDROGENS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Testosterone enanthate Testosterone cypionate Testosterone	Prostate cancer Breast cancer Lower Urinary Tract Symptoms (severe) Erythrocytosis Sleep apnea (severe, untreated) Heart failure (uncontrolled)	Prostate cancer Anaphylaxis Benign prostatic hyperplasia Erythropoiesis Venous thromboembolism Sodium retention Cardiovascular risks Oil based formulations: pulmonary oil microembolism (POME)	Cyclosporine → increased cyclosporine concentrations Warfarin → increased anticoagulant effects

CLINICAL USE & ADME

Androgen deficiency

Delayed puberty

Hypogonadism

Oral ingestion of testosterone rapidly catabolized via the liver

- Not an effective means of androgen replacement
- Oral formulations are available, but associated with increased liver tumors

Most preparations designed to bypass hepatic catabolism (injections, transdermal delivery systems)

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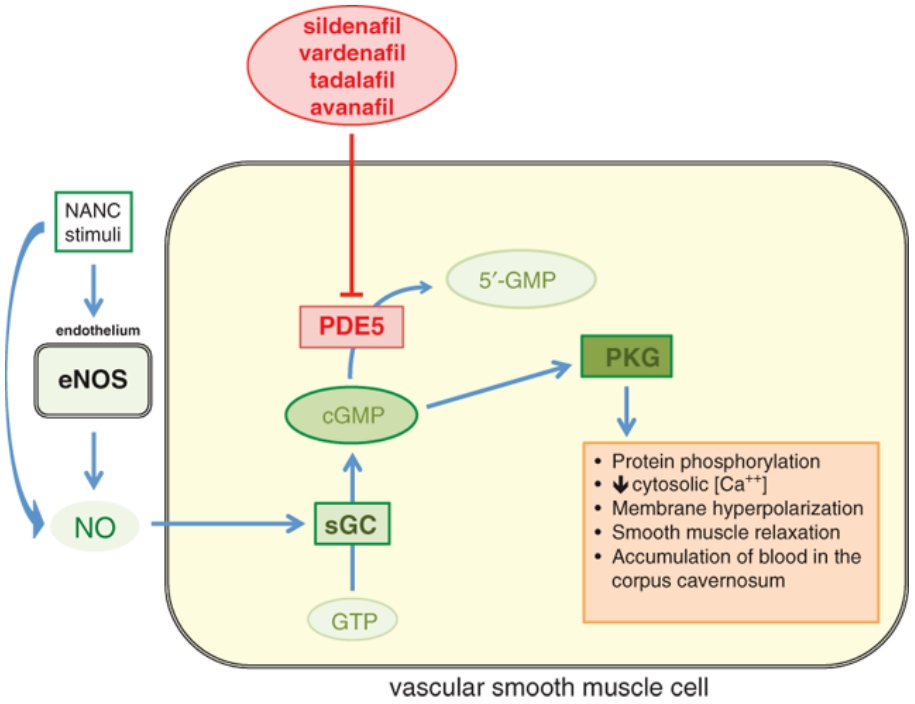
DRUGS FOR ERECTILE DYSFUNCTION

PHOSPHODIESTERASE-5 (PDE5) INHIBITOR MOA

Inhibit the enzyme PDE5 → prevention cGMP degradation → increased cGMP levels → enhanced activation of cGMP-dependent protein kinase (PKG) → PKG relaxes cavernosal smooth muscle → engorgement of corpus cavernosum with blood → erection



ACTIVE LEARNING

Based on what you now know about PDE5 inhibition, what side effects might you expect with their use?

ACTIVE LEARNING

Based on what you now know of PDE5 inhibition, what would you expect from concomitant use of nitrate vasodilators?

SELECTED PHOSPHODIESTERASE-5 (PDE5) INHIBITORS

Generic (Brand)	Contraindications & Cautions	Adverse Effects	Selected Interactions
Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Verdenafil (Levitra)	CI: **concurrent use of nitroglycerin or other nitrates,** guanylate cyclase stimulators (eg, riociguat)	Headache Flushing Dyspepsia Nasal congestion Dizziness Back pain Hypotension Blue-green tinting of vision (sildenafil, vardenafil)	CYP3A4 inducers → decreased PDE5i levels CYP3A4 inhibitors (eg, ritonavir, erythromycin) → increased PDE5i levels **Nitrates (severe hypotension)**

CINEMATIC REMINDER

https://www.youtube.com/watch?v=viK121c8iZI

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ANY QUESTIONS?

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