King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

MED 433 Teams

L1- Drugs Affecting Erectile Dysfunction

Objectives

- Revise the haemodynamic changes inducing normal erection
- Interpret its different molecular control mechanisms
- Define erectile dysfunction [ED] and enumerate its varied risks
- List drugs inducing ED and reflect on some underlying mechanisms
- Correlate drugs used in treatment of ED to the etiopathogenesis
- Classify oral 1st line therapy relevent to; Mechanism / Utility / ADRs
- Compare the pharmacological difference of PDE_5 inhibitors
- Study the transurethral, intracavernous or topical 2nd line therapies; Mechanism / Utility / ADRs
- Enumerate lines of treatment of priapism

Important to know

1-**Loss of lipido** ⟹ loss of desire
2- **Impotence** ⟹ Erectile Dysfunction
3- **Ejaculatory Dysfunction**
4- **Priapism** ⟹ **when** the erect penis does not return to its flaccid state

Mind Map

DRUGS AFFECTING ERECTILE DYSFUNCTION(ED)

- DRUGS ADVERSLY CAUSING ED
  - Centrally Acting Drugs
  - Centrally acting anti-hypertensives
  - Anti-hypertensives
  - Habituating Agents
  - Anti-androgens
- Peripheral Haemodynamic Changes Inducing ERECTION
- Drugs Treating ED
  - CENTRALLY
    - Androgens
    - Apomorphine
  - PERIPHERALLY
    - 1-PDE5 Inhibitors
    - 2-Prostaglandin Analogues
    - 3-Papaverine
    - 4-Phentolamine
- Treatment of Pripism

Introduction

A Male Sex Organ In most of the time exists in a Flaccid State **However**, during a sexual act the following events occur :

1- Desire

is provoked by brain (visual -olfactory -tactile-imagiative)all these send massages to hypothalamus to help in releasing testosteron and other mediators which provoke the desire

2- Arousal (erection)

Then by the descending tract (somatic supply :pudendal) (autonomic supply :cavernous n) PNS will be activated and SNS (alpha effects) will be inhibited + also, (DA,NE,Excitatory AA) help in erection

Erection is a parasympathetic over activity

(Erection) has The same meaning of (Tumescence)

During the sexual intercourse there will be sensory reflexes activate SNS causing Emission

Emission is a sympathetic over activity

3-ejaculation & Orgasm (occur in the same time)

Ejection of the semen by PSN and sensory afferents to the brain to initiate orgasm

ejaculation is a sympathetic over activity

4- Resolution

activation of SNS (alpha effects) and inhibition of PSN causing Flaccidity

Resolution is a sympathetic over activity

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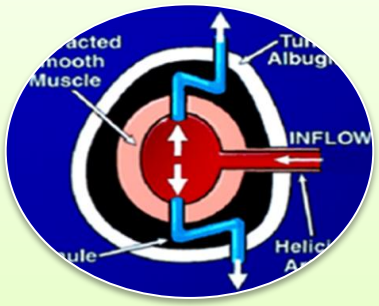
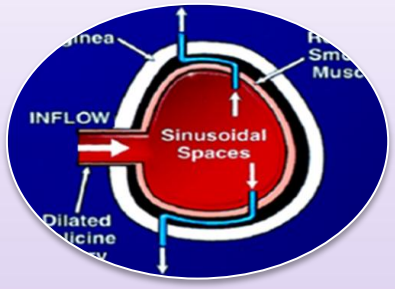
Introduction

Peripheral Haemodynamic Changes Inducing ERECTION



Flaccid state

1- blood sinusoid s are normal
2- smooth muscle is contracted
3- venous drainage is normal



Erect State

1- sinusoids are filled with blood
2- smooth muscle is relaxed
3- in pressure leading to block the venous drainage

Molecular control of erection :

1-Activation of **PSN** (cavernous n) which releases **Ach** that is going to work on endothelial cells to release endothelial nitric oxide

2- **Non adrenergic non cholinergic system** will be activated also to releases neuronal nitric oxide

{these two types of nitric oxide will work together on the vascular smooth muscle of sinusoids to activate sGC → cGMP → PKG leading to relaxation of VSMCs and erection (Tumescence)

4-Also VIP and Prostaglandins activate AC → cAMP → PKG to help in relaxation and erection

5- SNS (only the beta2 will be activated while alpha effects will be inhibited) which is vasodilator

So all these actions cause erection

Then after sexual intercourse end **SNS** will be activated (mainly alpha 1) causing constriction then flaccidity (Detumescence)

*VIP =vasointestinal peptide

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ED & DRUGS ADVERSLY CAUSING ED

Erectile Dysfunction :

Persistent or recurrent inability to attain (acquire) & maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance

Impotent is reserved for those men who experience erectile failure during attempted intercourse more than 75 % of the time.

the most common cause is endothelial dysfunction

1-Centrally Acting Drugs

As we said DA>NE promote arousal, so whenever 5HT act on $5HT_2$ →↓DA release →↓ arousal

1-Most ADDs→ ↓ 5HT uptake;

Like non-selectively as TCAs and selectively as SSRIs ↑ 5HT in synapse act on $5HT_2$ → ↓DA release →↓ arousal

NOTE: SSRIs also work Peripherally and antagonize NO actions ↓ genital sensation → Delay ejaculation → Treat Premature Ejaculation

2-Anti-psychotic drugs → DA antagonist + hyperprolact. → ↓ arousal →Erectile Dysfunction

3-Anti-epileptic drugs (phenytoin) → have GABA effect →antagonize Exc. a.a. → ↑ sedation → ↓ arousal

2-Centrally acting anti-hypertensives

1-Methyl dopa, Reserpine → ↓ arousal

2-Clonidine → arousal centrally / Vasoconstriction peripherally

3-anti-hypertensives

1-b2 blockers → -ve vasodilating b_2 + potentiate a_1 effect

2-Thiazide diuretics → ↓ spinal reflex controlling erection →↓ arousal

ADDs =antidepressants drugs
DA =dopamine

DRUGS ADVERSLY CAUSING ED

4-Anti-androgens (Affect testosterone release)

↓ Desire → ↓ arousal

1-Finasteride → a reductase inhibitor → irreversible erectile dysfunction

2-Cyproterone acetate → synthetic steroidal antiandrogen

3-Cimetidine (high doses) / Ketoconazole / Spironolactone → hyper- prolactinemia + gynecomastia

4-Estrogen-containing medications

5-Habituating Agents

1-Cigarette smoking → vasoconstriction + penile venous leakage

2-Alcohol [small amounts]→↑ desire +↓ anxiety + vasodilatation (small tendency to erection)

3-Alcohol [big amounts]→↑ sedation+ ↓ desire→ ↓ arousal

4-Chronic alcoholism→ hypogonadism + polyneuropathy

Drug Class	Specific drug examples
Beta-blockers Calcium-channel blockers Alpha-adrenergic agonists Cardiac glycosides	propranolol, metoprolol, atenolol verapamil, nifedipine clonidine digoxin
Thiazide diuretics Aldosterone antagonists	hydrochlorothiazide spironolactone
Fibric acid derivatives	gemfibrozil, clofibrate
Selective serotonin reuptake inhibitors Tricyclic antidepressants Other antidepressants	fluoxetine, sertraline, paroxetine, citalopram amitriptyline, desipramine, nortiptyline lithium
Benzodiazepines	lorazepam, alprazolam, diazepam
Histamine (H_2) receptor antagonists	ranitidine, cimetidine
Butyrophenones and phenothiazines	haloperidol, prochlorperazine, chlorpromazine
Hydantoin anticonvulsants	phenytoin
Cytotoxic agents	cyclophosphamide, methotrexate
Recreational drugs	alcohol, cocaine, marijuana

Drugs Treating Erectile Dysfunction

Centrally		Peripherally			
1-Androgens When Desire is lost	2-Apomorphine" It is dopamine agonist " When Arousal is lost	1-PDE5 Inhibitors •Sildenafil •Vardenafil •Tadalafil •Avanafil	2-Prostaglandin Analogues	3-Papaverine "It is PDE2,3,4 Inhibitors"	4-Phentolamine "It is a1 blocker "
Route of administation	ORAL		Intracavernosal Injection + Transurethral	Intracavernosal Injection	

All the drugs above cause vasodilation whatever the mechanism and all of them have the same efficacy but the route of administration and the medical condition of each patient is differ and that's how we chose between the drugs

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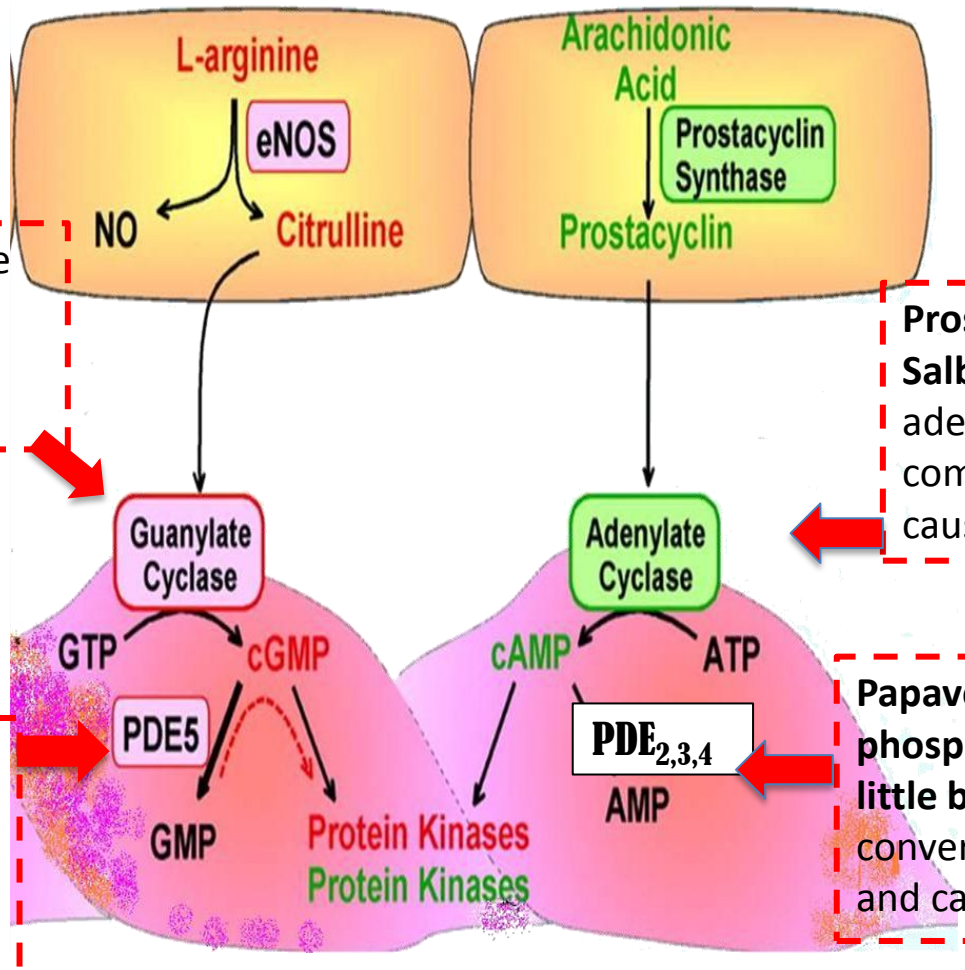
Drugs Treating Erectile Dysfunction



Nitrates activate Guanylate cyclase then complate the process and cause vasodilation

Prostaglandin Analogues and Salbutamol both activate adenylate cyclase then complate the process and cause vasodilation

Sildenafil and it's group act on **phosphodiesterase 5** and inhibte the conversion od cGMP into GMP and cause vasodilation

Papaverine acts on **phosphodiesterase 2,3,4 and little bit on PDE5** and inhibit the conversion of cAMP into AMP and cause vasodilation

Both **nitrates and salbutamol are not anymore used** these days because of the efficacy , they considered as weak drugs

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1-Selective PDE5 Inhibitors

drugs	**Sildenafil + Vardenafil + Tadalafil + Avanafil**
Route of Administration	**Oral and All drugs are given only once a day**
Mechanism	**Inhibit PDE_5 ➔ prevent breakdown of cGMP ➔ pertain vasodilatation ➔ erection** **They do not affect the lipido, so sexual stimulation is essential to a successful**
Pharmacodynamic Action (vasodilatation)	1. VSMCs of Erectile Tissue of Penis 2. VSMCs of (lung, brain) / heart 3. non-VSMCs (prostate, bladder, seminal vesicle, GIT) 4. Platelets and Other tissues; testis, sk. muscles, liver, kidney, pancreas
Indications	1. Erectile dysfunction; **1st line therapy**. All types have similar efficacy 2. Pulmonary hypertension 3. BPH & premature ejaculation 4. Others; CHF, Raynaud's disease, IBS…..etc *BPH=benign prostatic hypertrophy
Contraindications	1. Hypersensitivity to drug 2. Patients with history of AMI / stroke / fatal arrhythmias <6 month 3. Nitrates→ total contraindication / PDEIs in small dose + spacing at least 24hrs (48 hrs with *Tadalafil*) for fear of developing IHD/AMI due to severe hypotension

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1-Selective PDE5 Inhibitors

Side effect	**Common//** Headache +Flushing + Congestion 1. Dyspepsia and Myalgia & Back pain and ↓Sperm functions with Tadalafil 2. Abnormal vision with Sildenafil 3. Q-T prolongation with Vardenafil **less common //** 1. Ischemic Heart Disease & Acute Myocardial Infarction > patients on big dose or on nirates 2. Hypotension > patients on a-blockers than other antihypertensives 3. Bleeding; epistaxsis…..etc. 4. Priapism; if erection lasts longer than 4 hours → emergency situation **Rare//** 1. Ischemic Optic Neuropathy; can cause sudden loss of vision 2. Hearing loss
Pharmaco kinetic	**Absorption//**Fatty food interferes with **Sildenafil & Vardenafil** absorption → so taken on empty stomach / at least 2 hr.s after food **Tadalafil & Avanafil are not affected by food** **Metabolism//All by hepatic CYT3A4; Tadalafil** > the rest thus; ↑ADRs with enzyme inhibitors; erythro & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone…etc. ↓ efficacy with enzyme inducers; rifampicin, carbamazipine, phenytoin

Selectivity on PDE_5 is not absolute and vary with each drug **1- Can partially act on PDE targeting cGMP (6, 11, 9, 1) 2- In higher doses it can act on PDE targeting cAMP (2,3,4, 10,…)**

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1-Selective PDE5 Inhibitors

	Sildenafil	Vardenafil	Tadalafil
Time of administration before intercourse	1 hrs	1 hrs	1-12 hrs
Onset of action (min)	30-60 min	30-60 min	Less than 30-45 min
Duration of action (hrs.)	4 hrs	4-5 hrs	36 hrs
Precautions	1. **With a blockers [except tamsulosin]** →orthostatic hypotension 2. With hepato/renal insufficiency 3. **With Pyronie's disease=**deformity in male sex organ due to presence of fibrous tissue 4. With bleeding tendencies [leukemia's, hemophilia, Vit K deficiency, antiphospholipid syndrome,…etc] 5. With quinidine, procainamide, amiodarone **(class I & III antiarhtmics) (Vardenafil)** 6. Dose adjustment; when using drugs that have interaction on hepatic liver microsomal enzymes i.e inhibitors or inducers. 7. Retinitis pigmentosa=abnormality in the fields of vision		

NB. Avanafil has the advantage of been given 30 min before intercourse
Tadalafil must be given every 72 hrs if used with enzyme inhibitors

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2-Prostaglandin Analogues

drug	**Alprostadil**
Route of Administration	**Transurethral** Applied by a special applicator into penile urethra & acts on corpora cavernousa →Erection
Mechanism	**PG E1 → ↑cAMP** **Synthetic + more stable**
Efficacy	**Low - Intermediate Efficacy**
Side effect	1. **Variable penile pain** 2. **Urethral bleeding / Urethral tract infection** 3. **Vasovagal reflex / Hypotension** 4. Priapism or Fibrosis →rare

3-other (Topical)

Drugs	20% **Papaverine**; ↑cAMP + cGMP 2% **Minoxidil**; NO donner + K channel opener 2% **Nitroglycerine + a drug absorption enhancers**
Side effect	**Female Partner can develop** → hypotension, headache → vaginal absorption.
Efficacy	**Low efficacy / No FDA approval**

3-other (oral)

Drugs	Testosterone
Indications	1. Given to those with hypogonadism or hyperprolactenemia 2. Given for promotion of desire

Drugs	Apomorphine
Route of Administration	Given sublingual / Acts quickly.
Mechanism	1. A dopamine agonist on D_2 receptors. (n. paraventricularis) 2. Activates arousal centrally; Erectogenic + Little promotion of desire
Indications	mild-moderate cases / psychogenic / PDE_5 Is contraindication
Side effect	nausea, headache, and dizziness but safe with nitrate
Efficacy	Not FDA approved / Weaker than PDE_5 Is

Oral phentolamine	a_1 blocker / debatable efficacy
Yohimbine	Central and periphral a_2 agonist → Aphrodetic + Erectogenic but low efficacy and many CV side effects Aphrodetic = provoke the desire
Trazodone	Antidepressant, a 5HT reuptake inhibitor (has alpha blocking action causing relaxation)→ priapism
Korean Ginseng	Questionable / may be a NO donner

3-other (Intracavernosal Inj)

Drugs	**Alprostadil**
Route of Administration	Intracavernosal Inj Needs training → Erection → after 5-15 min → lasts according to dose injected May develop fear of self injury / Discontinuation
Mechanism	PG E1 → ↑cAMP
Side effect	1. Pain or bleeding at injection site 2. Cavernosal fibrosis 3. Priapism 4. Urethral tract infection

Drugs	**Papaverine**
Route of Administration	Intracavernosal Inj
Mechanism	**PG E1 → ↑cAMP+ cGMP**

Drugs	**Phentolamine**
Route of Administration	Intracavernosal Inj
Mechanism	**α_1 blocker**

All of the 3 drugs can be **combined in severe cases**

Treatment of Pripism

- **A medical emergency**
- **Aspirate blood to decrease intracavernous pressure.**
- **Intracavernous injection of Phenylephrine → a_1 agonist → detumescence**

a_1 antagonist Cause → Pripism

a_1 agonist Treat → Pripism

SUMMARY

DRUGS	Mechanism	ROA	USES	SIDE EFFECTS
PDE5 Inhibitors **•Sildenafil**	**Inhibit PDE_5 → prevent breakdown of cGMP**	**ORAL**	1. Erectile dysfunction; 2. Pulmonary hypertension 3. BPH & premature ejaculation	1. Headache +Flushing + Congestion 2. IHD & AMI 3. Hypotension 4. Priapism
Alprostadil	**PG E1 → ↑cAMP**	Intracavernosal Inj + Transurethral	Erectile dysfunction;	1. Pain or bleeding at injection site 2. Cavernosal fibrosis 3. Priapism 4. Urethral tract infection
Papaverine	BOTH ↑cAMP + cGMP	Intracavernosal Inj	Erectile dysfunction;	**WHEN use it topically** **Female Partner can develop** → hypotension, headache → vaginal absorption.
Apomorphine	**A dopamine agonist on D_2 receptors**	**ORAL (sublingual)**	**mild-moderate cases / psychogenic \ PDE_5 Is contraindication**	**nausea, headache, and dizziness but safe with nitrate**

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SUMMARY

DRUGS	Mechanism	ROA	USES	SIDE EFFECTS
phentolamine	**α_1 blocker**	**ORAL+**Intracavernosal Inj	Erectile dysfunction;	_____
Testosterone	_____	**ORAL**	1. Given to those with hypogonadism or hyperprolactenemia 2. Given for promotion of desire.	_____

Quiz yourself

Q1/ A male patient came to the clinic complaining that he lack saxeual desire, the problem lies with :

A. minoxidil
B. Testosterone hormone
C. Dihyrotesteosteron
D. GTH

Q2/ Which of the following is one of the mechanism that can cause impotence :

A. Incrase in B2 activity
B. Activation of PE1
C. Decrease dopamine
D. Increase the ACH

Q3/ Which one of the following anti-depressing drugs doesn't affect the dopamine release :

A. TCAs
B. Serotonin antagonist
C. Norepinephrine reuptake inhibitors
D. Norepinephrine dopamine reuptake inhibitors

Q4/ which one of the following is one of <u>Alprostadil</u> side effect :

A. Hypotension
B. Nausea
C. Epistaxsis
D. Female partner headache

Q5/ Which of the following is <u>slidenatil</u> mechanism of action :

A. Inhibit the converging of cGMP to GMP by acting on PDE5
B. Inhibit the converging of cAMP to AMP by acting on PDE3
C. Block a1 receptor
D. Act on PE1 and increase cAMP

Q6/ Which one of the following drugs can cause urethral tract infection as an adverse effect for using it :

A. Testosterone
B. Sildenafil
C. Alprostadil
D. minoxidil

Q7/ For priapism treatment we give :

A. Inj. Of phenylephrine
B. Intracavernous inj. Of papaverine
C. Intracavernous inj. Of phentolamine
D. Intracavernous inj. Of alprostadil

Q8/ Which of the following drugs is contraindicated with pyronie's disease :

A. Apomorphine
B. Sildenafil
C. Papaverine
D. alprostadil

Answers 1.b 2.c 3.a 4.a 5.a 6.c 7.a 8.b

Done by

PHARMACOLOGY 433

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