ALPHA BLOCKERS

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Alpha Blockers | Mechanism of Action, Indications, Adverse Reactions, Contraindications

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OUTLINE

I) INTRODUCTION

- There are 2 types of alpha receptors: alpha-1, alpha-2

(A) ALPHA-1 RECEPTORS

- Most important locations:
  - Smooth Muscles of Blood vessels
  - Prostatic smooth muscle
  - Internal Urethral Sphincter
- Epinephrine (Epi) and Norepinephrine (NE) bind to the Alpha-1-Receptors
- Blood vessels
  - Epi/NE → binds to alpha-1 receptor → vasoconstriction → ↑TPR (Total peripheral Resistance) →↑Afterload and ↑Blood pressure (BP)
  - Alpha blockers → Inhibit Epi/NE binding to Alpha-1 receptors → Vasodilation →↓TPR →↓Afterload and ↓BP
- Prostatic Smooth Muscle
  - Epi/NE → binds to alpha-1 receptor → prostatic muscle contraction →↑Prostatic Fluid (Component of Semen)
  - Sympathetic → Ejaculation (Shoot)
  - Parasympathetic→ Erection (Point)
  - Alpha blockers → Inhibit Epi/NE binding to Alpha-1 receptors → ↓Prostatic Fluid
- Internal Urethral Sphincter
  - Epi/NE → binds to alpha-1 receptor →contraction of the sphincter →↓Urine flow → ↑Urine retention
  - Alpha blockers → Inhibit Epi/NE binding to Alpha-1 receptors → Relax Internal Urethral Sphincter → ↑Urine flow→↓ Urine retention
  - In patients who have BPH, and the Prostate becomes really large (size of Grapefruit) →obstruct urinary outlet → Alpha blockers can relax the smooth muscle of the sphincter and allow urine flow
  - BPH = Benign prostatic Hypertension

(B) ALPHA-2 RECEPTORS

- Location: Presynaptic adrenergic nerve terminals
- Mechanism of action:
  - Gi protein → Inhibit Adenylyl Cyclase (AC) →↓cAMP→ inhibit protein kinase activity
- Role: Negative Feedback Control
  - NE→ binds to α_2-receptors →↓release NE from the nerve terminal

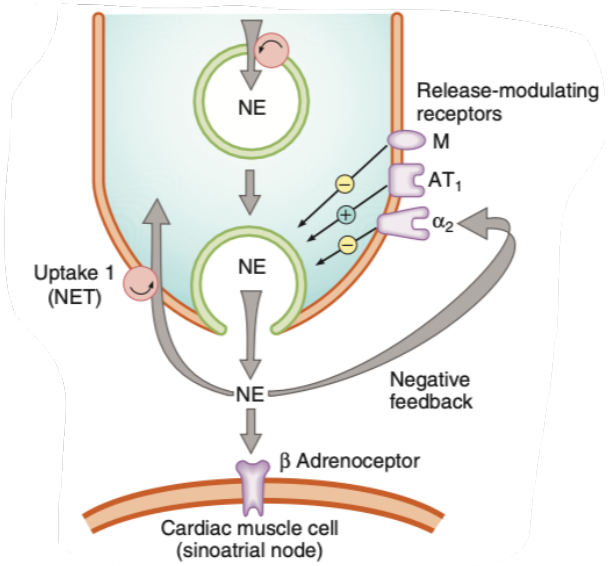

Figure 1.Noradrenergic Nerve Terminal (Trevor et al., 2018).

(C) ALPHA RECEPTORS ANTAGONISTS

Selective Alpha-1 Blockers

- Inhibit α_1-Receptors
  - Terazosin
  - Prazosin
  - Tamsulosin
  - Doxazosin

Non-Selective Alpha Blockers

- Block α_1 and α_2 Receptors
  - Phenoxybenzamine - Allosteric Inhibitor
  - Phentolamine – Active Site Inhibitor

II) MECHANISM OF ACTION OF ALPHA BLOCKERS

(A) SELECTIVE ALPHA-1 BLOCKERS

- Inhibit α_1-Receptors
  - Terazosin
  - Prazosin
  - Tamsulosin
  - Doxazosin
- How does a smooth muscle contract?
  - Calcium enters the cell through calcium channels→ Ca^{2+} binds to Calmodulin → Ca^{2+}-Calmodulin activates MLCK (Myosin light-chain Kinase) → Phosphorylation of Myosin → Phosphorylated myosin enables Cross-Bridge Formation with Actin → Contraction Figure 2
  - Epi/NE → binds to alpha-1 receptor → G-protein →GDP replaced with GTP → activate Phospholipase C → binds to PIP2→ IP3 & DAG
    - IP3 →↑ Ca^{2+} release from Smooth Endoplasmic Reticulum →Ca^{2+} binds to Calmodulin → Ca^{2+}-Calmodulin → activate a protein Kinase
    - DAG→ activate Protein Kinase C (PKC)
  - Protein Kinase produced from either pathway can activate MLCK and cause Smooth Muscle Contraction

- Alpha-1 blockers Inhibit the Epi/NE from binding to the receptor→ Inhibit Ca^{2+} release and activation of kinases→ MLCK not activated → Relaxation of Smooth muscle

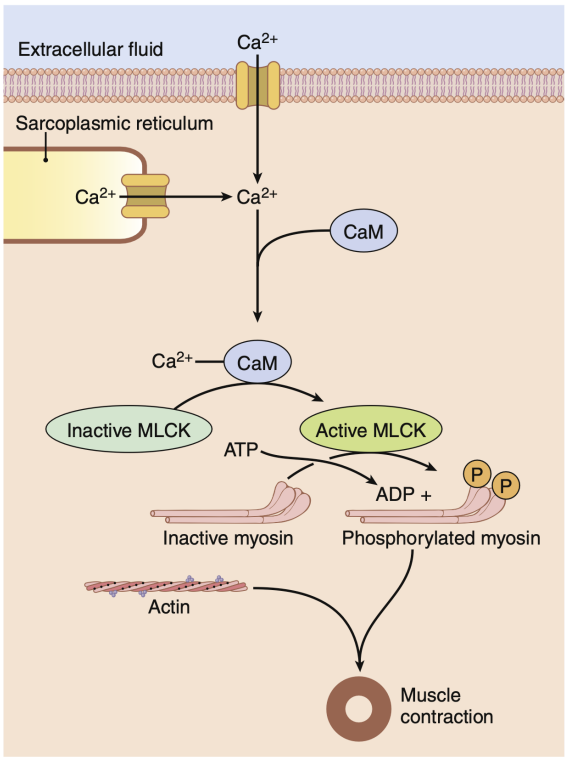

Figure 2.Smooth Muscle contraction (Hall & Hall, 2020).

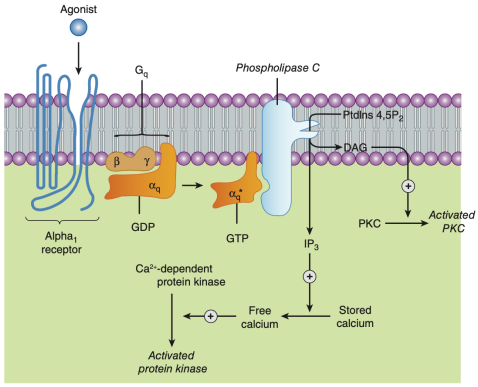

Figure 3. Alpha-Receptor Mechanism (Katzung, 2017).

(B) NONSELECTIVE ALPHA BLOCKERS

(1) Phenoxybenzamine

- Irreversible inhibitor-Allosteric Inhibitor
  - Binds to the allosteric site → Conformational change of the receptor → Epi, NE are not able to bind to the receptor (even in high concentration)

(2) Phentolamine

- Reversible inhibitor- Competitive inhibitor
  - Binds to the active site (the site where Epi, NE bind) → inhibits Epi, NE from binding
- If there is high concentration of Epi, NE → Competition over binding to the active site→ Epi/NE may bind to the receptor
- In pheochromocytoma there is a high concentration of Epi/NE due to the tumor in adrenal medulla.

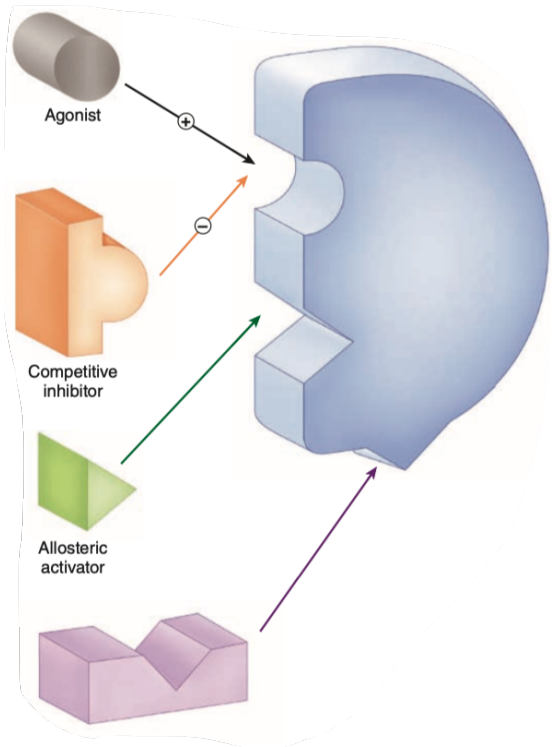

Figure 4. Different ways to interact with receptors (Katzung, 2017).

III) INDICATIONS

(1) Hypertension

- Second-line drugs in hypertension therapy
- Good choice in HTN+ BPH

(2) BPH

- Urine retention secondary to BPH

- Terazosin
- Doxazosin
- Tamsulosin

BPH

Most men will develop benign prostatic hyperplasia (BPH), which can be associated with lower urinary tract symptoms (LUTS). The common clinical manifestations of LUTS/BPH include storage symptoms (increased daytime frequency, nocturia, urgency, and urinary incontinence) and voiding symptoms (slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void). Symptoms vary in severity over time and do not correlate well with prostate size or physiologic abnormalities.
It is suggested that all men with lower urinary tract symptoms (LUTS)/BPH be instructed in lifestyle interventions. These should be tailored to symptoms but may include avoiding fluids prior to bedtime or before going out, reducing consumption of mild diuretics such as caffeine and alcohol, and double voiding to empty the bladder more completely.
Men with LUTS/BPH can be treated with one or more classes of medications and, in general, should try medical treatment prior to considering surgical interventions.
For most patients, initiate monotherapy with an alpha-1 adrenergic antagonist for initial treatment [UpToDate, 2021] .

(3) Distal Ureteral Stones

- Calculi in Ureter

- Alpha blockers → relax the smooth muscle → dilate ureter lumen → pass the stone

- Tamsulosin (Flomax®)

(4) Pheochromocytoma

- Tumor in Adrenal Medulla → ↑↑Epi, NE→ ↑ BP
- Phenoxybenzamine

Pheochromocytoma

A pheochromocytoma is a catecholamine-secreting tumor that typically develops in the adrenal medulla. Pheochromocytomas are usually benign (~ 90% of cases) but may also be malignant. Classic clinical features are due to excess sympathetic nervous system stimulation and involve episodic blood pressure crises with paroxysmal headaches, diaphoresis, heart palpitations, and pallor. However, pheochromocytomas may also be asymptomatic or manifest with persistent hypertension. Elevated catecholamine metabolites in the plasma or urine confirm the diagnosis, while imaging studies in patients with positive biochemistry are used to determine the location of the tumor. Surgical resection is the treatment of choice but is only carried out once alpha-adrenergic blockade with phenoxybenzamine has become effective [AMBOSS,2021] .

(5) Hypertensive Emergencies

Ingestion of sympathomimetic agents:

- MAO-I + Tyramine (cheese, wine)
  - Taking tyramine-containing foods in patients who take chronic monoamine oxidase inhibitors
  - Phentolamine
- Amphetamine-like compounds, Cocaine
  - Phentolamine
  - Phenoxybenzamine

- Hypertensive crisis (acute severe hypertension): an acute increase in systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 120 mm Hg [AMBOSS,2021]
- Hypertensive urgency: hypertensive crisis that is either asymptomatic or with isolated nonspecific symptoms (e.g., headache, dizziness, or epistaxis) without signs of organ damage [AMBOSS,2021]
- Hypertensive emergency: hypertensive crisis with signs of end-organ damage, mainly in the cardiovascular, central nervous, and renal systems [AMBOSS,2021]

IV) ALPHA BLOCKERS SIDE EFFECTS

Hypotension

- Vasodilation→ ↓TPR→↓BP

Orthostatic Hypotension

Orthostatic hypotension is a common side effect of medications, particularly antihypertensive agents (ex. **Alpha-1 blockers**, Beta blockers, Diuretics, ACE inhibitors, Alpha-2 Agonists, etc.) [UpToDate, 2021]

Many medications can precipitate or exacerbate symptoms of orthostatic hypotension through a variety of mechanisms, **including peripheral vasodilation**, autonomic dysfunction, and volume depletion. [UpToDate, 2021]

Flushing

- Vasodilation near skin surface → Flushing

Edema

- Vasodilation→↑ Capillary permeability→ Fluid leakage in the interstitial spaces → Edema (commonly in the periphery, extremities)
- Vasodilation→ ↓TPR→↓BP→↓Kidney Perfusion→↑ Renin → ↑ Angiotensin-II → Aldosterone → ↑ Water and sodium reabsorption →↑ BV (Blood Volume) → Fluid leakage in the interstitial spaces → Edema

Reflex Tachycardia

- Vasodilation→ ↓TPR→↓BP → activate Baroreceptor Reflex (Aortic and Carotid Sinus) →↑SNS (Sympathetic Nervous System) →↑HR = Reflex Tachycardia

- **Blocking alpha-2 receptor** (Phenoxybenzamine, Phentolamine) →Inhibit Negative Feedback control→ ↑NE release from postsynaptic neuron → effects on multiple organs
  - Heart: ↑NE→ Stimulate SA, AV node→↑HR ↑AV conduction → **Reflex Tachycardia**

Intraoperative floppy iris syndrome (IFIS)

- Eye: stimulation of Alpha-1 receptor on the Pupillary Dilator muscle in the Iris→ contraction → dilation of the pupil → Mydriasis
  - Alpha blockers → pupil constriction →Miosis
- **Intraoperative floppy iris syndrome (IFIS)**
  - Cataract surgery → incision in cornea
  - If the patient is on alpha blockers especially "Tamsulosin" → miosis → prolapsing Iris through the corneal incision which is called =Intraoperative floppy iris syndrome (IFIS)

Urinary Frequency

- As a result of relaxing internal urethral Sphincter
- Possibility of Urinary Incontinence
- External Urethral Sphincter= voluntary Control of the urination (Micturition)

For micturition to occur, three things must happen simultaneously:

- the detrusor must contract,
- the internal urethral sphincter must open,
- the external urethral sphincter must open. [Marieb & Hoehn, 2012]

Retrograde Ejaculation

- Alpha blockers→ Relaxation of Internal Urethral Sphincter → Semen flows upward from common ejaculatory duct into the bladder
- Also, common side effect of Prostatic surgery

↓ Ejaculatory Response

- Alpha1 Receptor on the vas deferens→ Alpha blockers→ Relax smooth muscle →↓ ejaculatory response

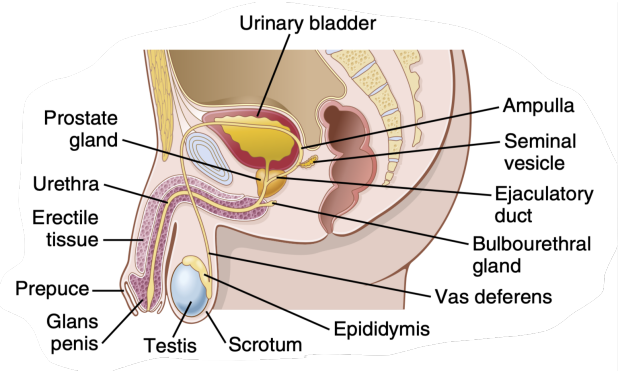

Figure 5. Male reproductive system (Hall & Hall, 2020).

V) CONTRADICTIONS

- Tamsulosin in Cataract surgery
- Urinary Incontinence

VI) REVIEW QUESTIONS

1) **A 56-year-old man has hypertension and an enlarged prostate, which biopsy shows to be benign prostatic hyperplasia. He complains of urinary retention. Which of the following drugs would be the most appropriate initial therapy?** [Trevor et al., 2018]
   a. Albuterol
   b. Atenolol
   c. Metoprolol
   d. Prazosin
   e. Timolol

2) **When given to a patient, phentolamine blocks which one of the following?** [Trevor et al., 2018]
   a. Bradycardia induced by phenylephrine
   b. Bronchodilation induced by epinephrine
   c. Increased cardiac contractile force induced by norepinephrine
   d. Miosis induced by acetylcholine
   e. Vasodilation induced by isoproterenol

3) **A patient presents at the emergency department with threatened anaphylaxis. Respiratory obstruction appears likely if she is not treated immediately. Her past medical history includes hypertension, for which she is receiving an adrenoceptor blocker. The emergency physician plans to use epinephrine to treat her anaphylactic reaction. Which of the following effects of epinephrine would be blocked by prazosin but not by metoprolol?** [Trevor et al., 2018]
   a. Cardiac stimulation
   b. Increase of cAMP (cyclic adenosine monophosphate) in fat cells
   c. Mydriasis
   d. Relaxation of bronchial smooth muscle
   e. Relaxation of the uterus

CHECK YOUR ANSWERS

VII) REFRENCES

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