ALPHA BLOCKERS

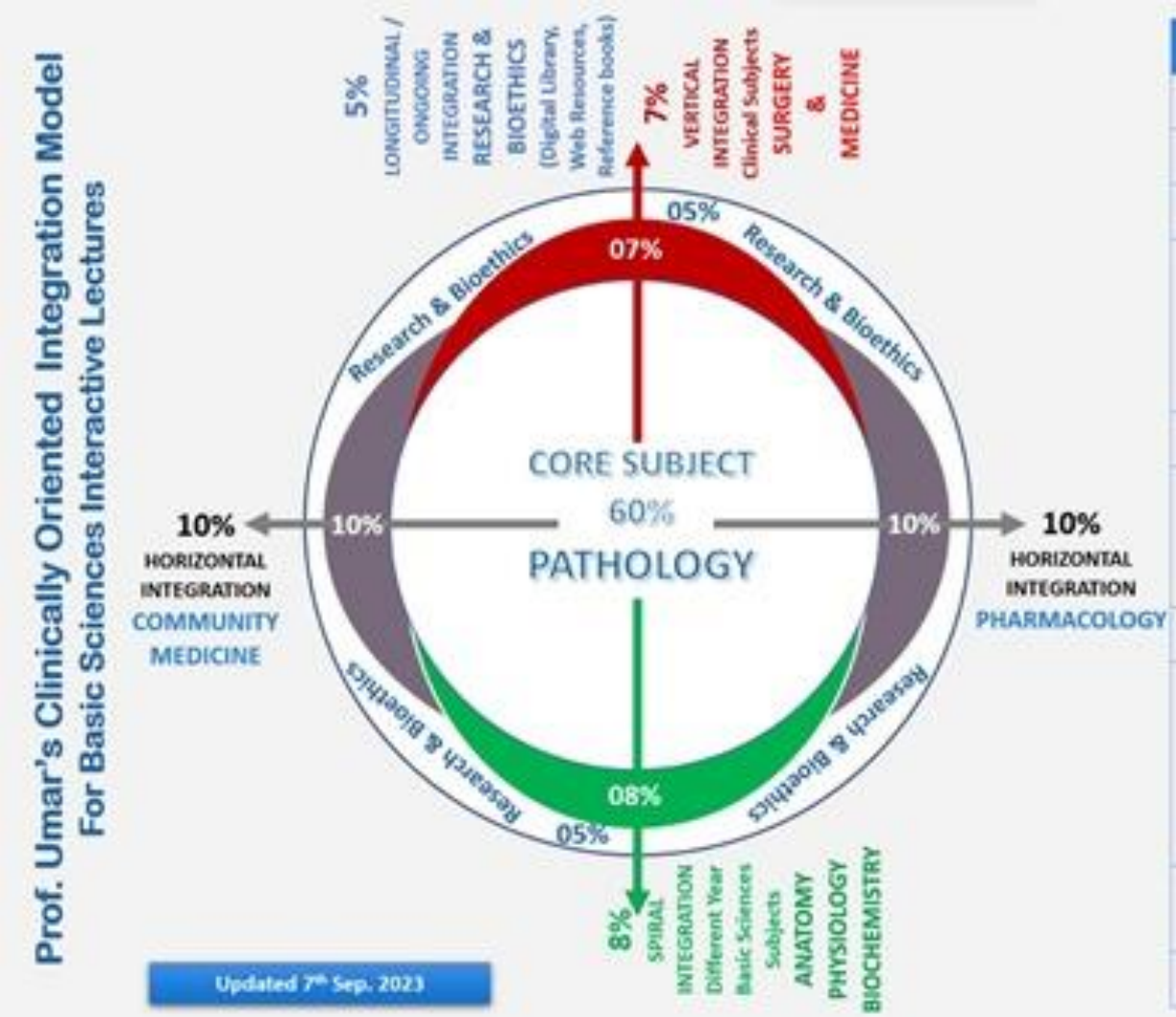
Dr. Zunera Hakim

- Katzung's Basic & Clinical Pharmacology, 15th Edition
- Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

VISION & MOTO

- **To impart evidence based research oriented medical education**
- **To provide best possible patient care**
- **To inculcate the values of mutual respect and ethical practice of medicine**

UMAR'S MODEL OF INTEGRATION



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

Learning Objectives

At the end of the lecture, students of 3rd Year MBBS will be able to ;

01 **Classify alpha adrenergic blockers**

02 **Describe the mechanism of action and therapeutic uses of alpha adrenergic blockers**

03 **Discuss adverse effects of alpha adrenergic blockers**

04 **Explain the basis of " epinephrine reversal"**

ADRENOCEPTOR ANTAGONISTS

Agents that inhibit responses mediated by adrenoceptor activation are called a**drenoceptor antagonists, adrenergic antagonists or adrenergic blocking agents (α and β adrenergic antagonists)**

These agents reduce the effects produced by both **sympathetic nerve stimulation** and by **exogenously administered adrenomimetics**

CLASSIFICATION ACCORDING TO REVERSIBILITY OF ACTION (Duration of Action)

Reversible (Competitive blockers- short acting)

- Prazosin
- Terazosin
- Trimazosin
- Doxazosin
- Urapidil
- Phentolamine
- Tolazoline

Irreversible (Non-Competitive blockers-long acting)

Phenoxybenzamine

ACCORDING TO RECEPTOR SELECTIVITY

A. Selective α-Blockers

i) Selective α_1 Blockers
Prazosin
Doxazosin
Alfuzosin
Terazosin
Bunazocin
Tamsulosin
Urapidil
Indoramin

ii) Selective α_2 Blockers
Yohimbine
Tolazoline

CLASSIFICATION

CORE

ACCORDING TO RECEPTOR SELECTIVITY

B. **Non-selective / Both α_1 & α_2 Blockers**

Phentolamine
Phenoxybenzamine
Dibenamine

C. **Mixed α and β Blockers**

Labetalol
Carvedilol

D. **Drugs with α blockade as adverse effect**

Neuroleptic drugs
(Chlorpromazine , Haloperidol)
Antidepressant (trazodone)
Ergotamine
Dihydroergotamine

CLASSIFICATION

CLASSIFICATION ACCORDING TO GENERATIONS

First Generation (Non selective)

Phentolamine
Phenoxybenzamine

Second Generation

Terazosin
Doxazosin
Alfuzosin*

Third Generation

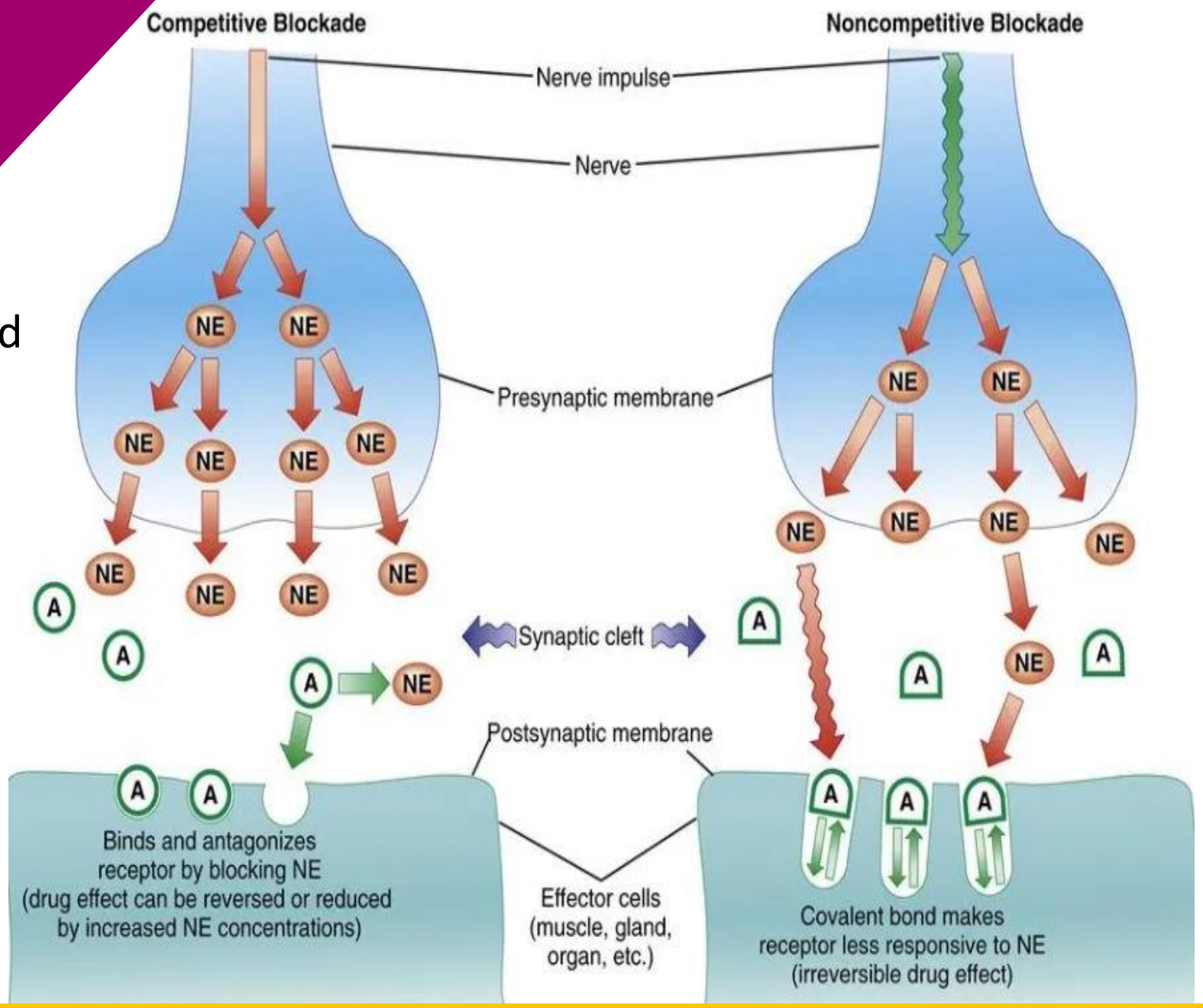
Tamsulosin
Silodosin

LOCATION OF ALPHA ADRENOCEPTORS

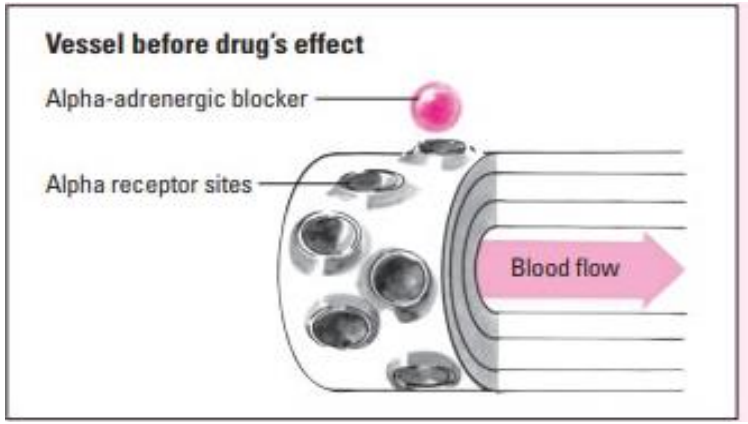
Receptor	Effects	Tissue Localization
α_1 Type	↑IP3, DAG Common to all	
α_{1A}		Arterial smooth muscle, urethral smooth muscle ,heart, liver, lung, cerebellum, cerebral cortex, prostate, vas defers
α_{1B}		Kidney, spleen, aorta, lung, cerebral cortex, venous smooth muscle
α_{1D}		Aorta, cerebral cortex, prostate, hippocampus, bladder neck, detrusor smooth muscle
α_2 Type	↓cAMP; common to all	
α_{2A}	↓cAMP; ↑K^+ channels; ↓ Ca^{2+} channels	Platelet, cerebral, cortex, locus ceruleus, spinal cord
α_{2B}	↓cAMP;↓ Ca^{2+} channels	Liver, kidney
α_{2C}	↓cAMP	Cerebral cortex

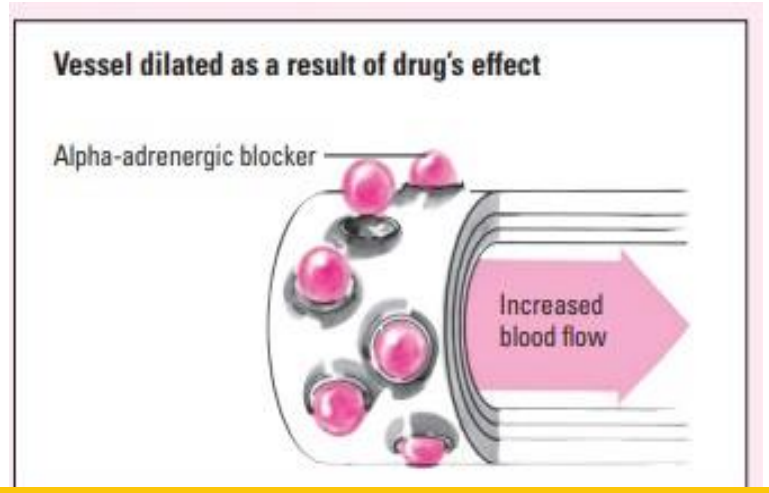
MECHANISM OF ACTION

- Prevention of α receptor mediated events through
  - Reversible blockade
  - Irreversible blockade
- Inhibition of uptake of NE by presynaptic adrenergic terminal
- Action at other receptors (5HT, histamine & acetylcholine)



PHARMACOLOGICAL ACTION



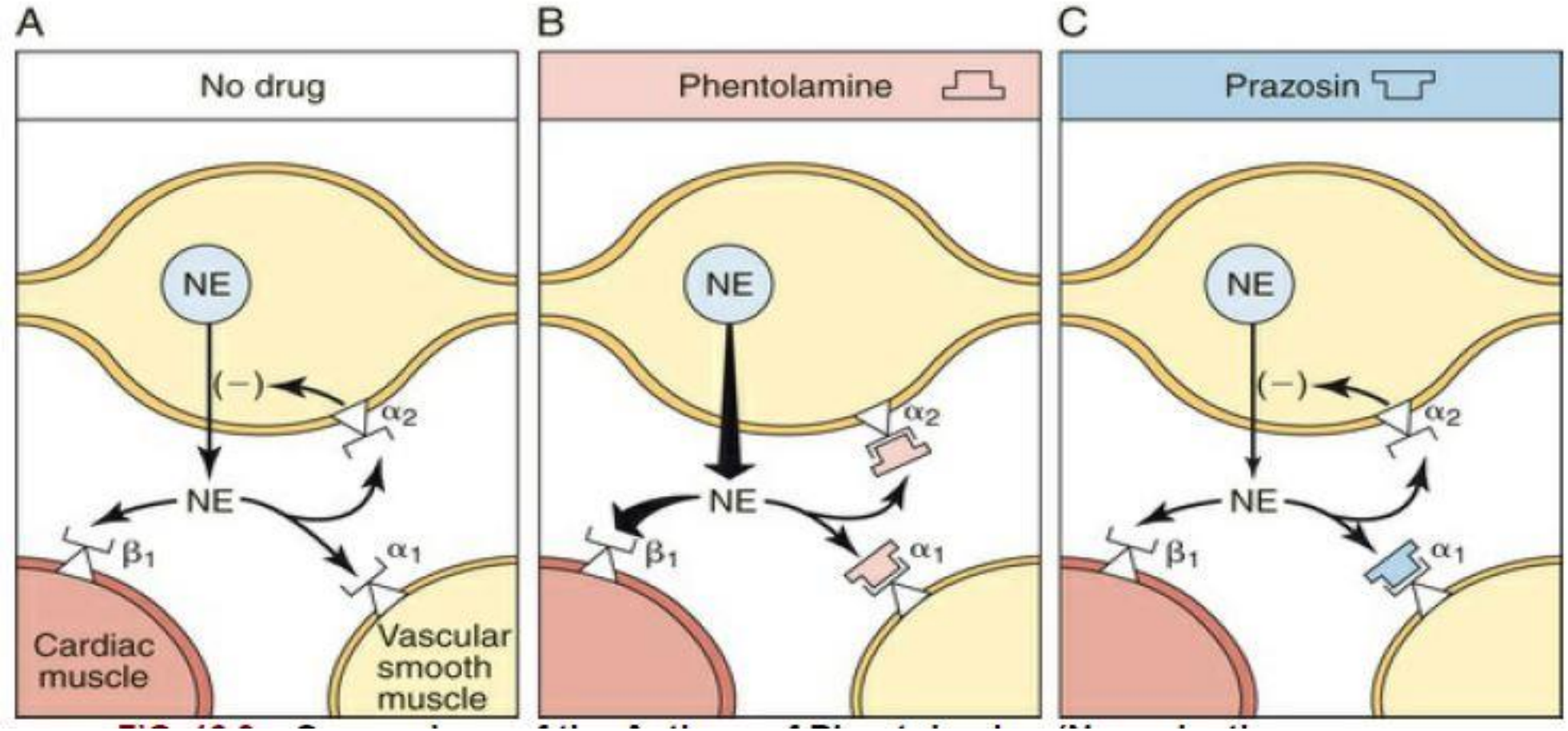


CARDIOVASCULAR SYSTEM

- Inhibit the **vasoconstrictor** effect of norepinephrine by **selectively** inhibiting the activation of **postsynaptic α1 (arteries & veins)** receptors by circulating and/or neutrally released catecholamines
- This results in fall in peripheral vascular resistance ensuing drop in BP
- Due to blockade of **α1** receptors in veins of lower limbs dilatation →↓ venous tone → pooling of blood on standing Postural / orthostatic Hypotension → dizziness, fainting syncope
- Reflex tachycardia due to baroreceptor reflexes
- More marked if presynaptic **α2** receptors in the heart are blocked leading to more stimulation of heart by NE

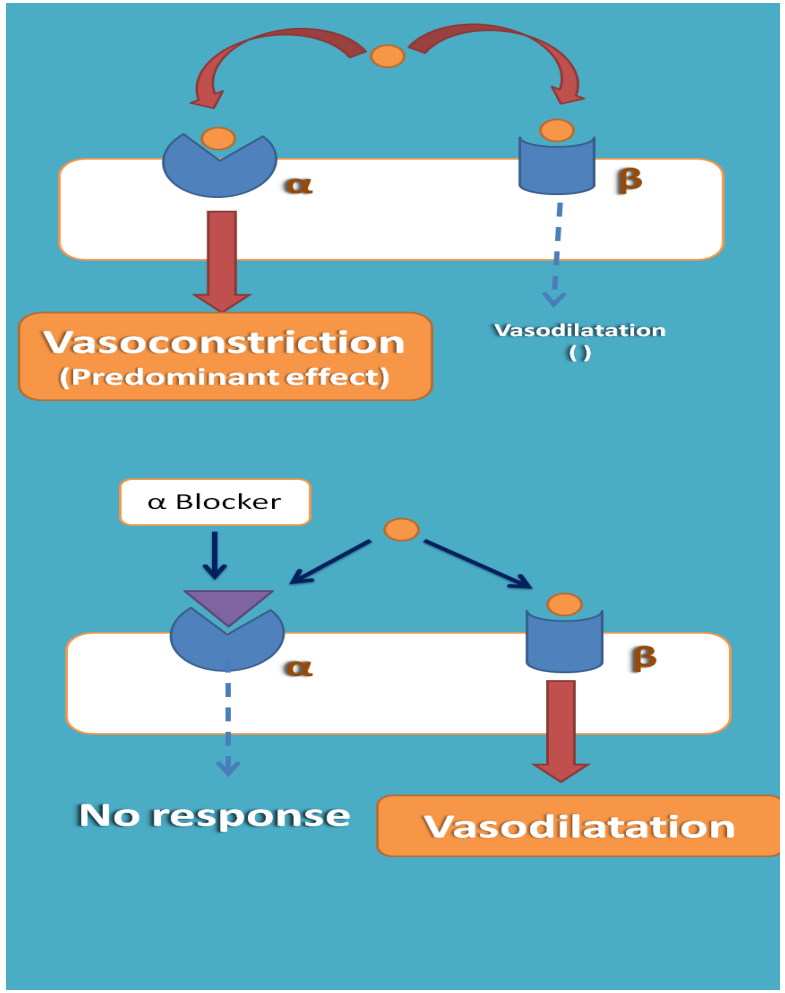
PHARMACOLOGICAL ACTION

CARDIOVASCULAR SYSTEM



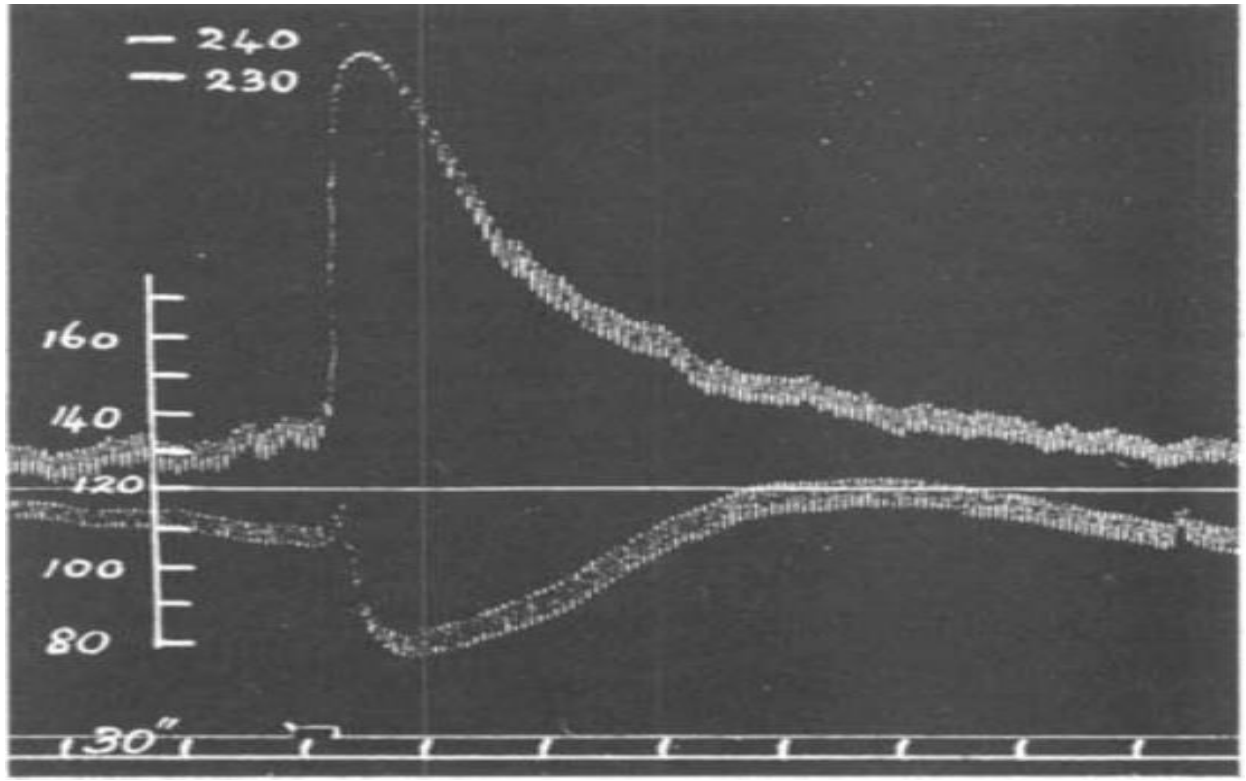
PHARMACOLOGICAL ACTION

CARDIOVASCULAR SYSTEM

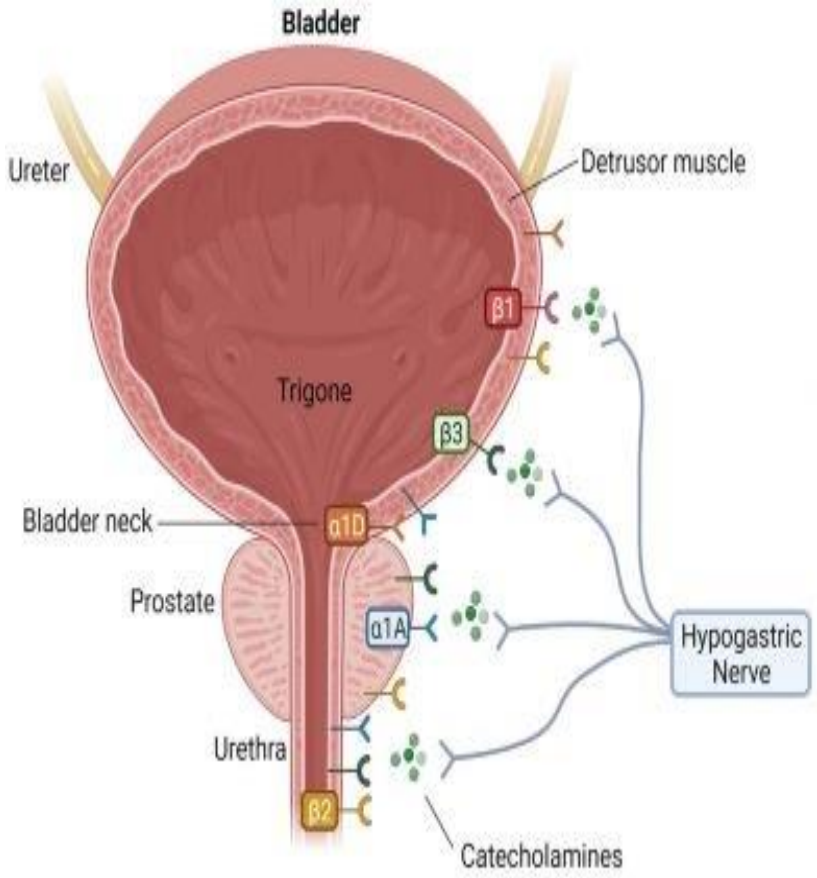


EPHINEPHRINE REVERSAL PHENOMENON OF DALE

Reversal in the effect of large doses of epinephrine on blood pressure from a pressor response mediated by α_1 receptors to a depressor response, mediated by β_2 receptors by prior administration of α blocker.



PHARMACOLOGICAL ACTION



Urinary bladder:

Blockade of α_{1A} & α_{1D} receptors in prostate ---

Decreased smooth muscles tone in prostate and neck of bladder ---- ↑ urine outflow

Apoptosis in prostate smooth muscle

Metabolic Effects:

↑ insulin secretion from islet cells (α_2 blockers)

Eye:

Miosis (α1 pupillary dilator muscle)

Other Effects:

↑ HDL

Nasal stuffiness

↑ intestinal motility

THERAPEUTIC USES

❖ Selective α Adrenergic Blockers

α_1 Adrenergic Blockers

1. Urinary Obstruction (Benign Prostatic Hyperplasia)
2. Chronic Hypertension
3. Hypertensive Emergencies
4. Peripheral Vascular Spastic Disease
5. Congestive Cardiac Failure

α_2 Adrenergic Blockers

1. Postural Hypotension
2. Diabetic Neuropathy

❖ Non selective α Adrenergic Blockers

1. Pheochromocytoma
2. Local vasoconstrictor excess
3. Reversal of tissue anesthesia
4. Sexual dysfunction

ADVERSE EFFECTS

❖ Selective α Adrenergic Blockers

- Postural Hypotension & syncopal episodes
  First dose phenomenon
- QT interval prolongation (Alfuzosin)
- Intraoperative floppy iris syndrome (Tamsulosin)
- Retrograde ejaculation

❖ Non selective α Adrenergic Blockers

- Hypotension
- Reflex Cardiac stimulation (tachycardia, arrhythmias and MI)
- Nasal stuffiness and congestion
- Nausea
- Sedation

  } Phenoxybenzamine

- Diarrhea (Phentolamine)
- Retrograde ejaculation

RESEARCH

Perez, D.M., 2022. Targeting Adrenergic Receptors in Metabolic Therapies for Heart Failure: A Review. *Current Practice in Medical Science Vol. 3*, pp.1-34.

BIOETHICS

Kim, S.J., Park, S.G., Pak, S., Lee, Y.G., Cho, S.T. and Kwon, O., 2022. Predictive factors for alpha blocker use after transurethral prostatectomy: Can preoperative urodynamic outcome predict alpha blocker medication after surgery?. *Plos one*, *17*(9), p.e0274399.

ARTIFICIALINTELLIGENCE

Deluigi, M., Morstein, L., Schuster, M., Klenk, C., Merklinger, L., Cridge, R.R., de Zhang, L.A., Klipp, A., Vacca, S., Vaid, T.M. and Mittl, P.R., 2022. Crystal structure of the α1B-adrenergic receptor reveals molecular determinants of selective ligand recognition. *Nature Communications*, *13*(1), p.382.

END OF LECTURE ASSESSMENT

A 38-year-old man has been experiencing palpitations and headaches. He enjoyed good health until 1 year ago when spells of rapid heartbeat began. These became more severe and were eventually accompanied by throbbing headaches and drenching sweats. Physical examination revealed a blood pressure of 150/90 mm Hg and heart rate of 88 bpm. During the physical examination, palpation of the abdomen elicited a sudden and typical episode, with a rise in blood pressure to 210/120 mm Hg, heart rate to 122 bpm, profuse sweating, and facial pallor. This was accompanied by severe headache. What is the likely cause of his episodes? What caused the blood pressure and heart rate to rise so high during the examination? What treatments might help this patient?

END OF LECTURE ASSESSMENT

The patient had a pheochromocytoma. This tumor secretes catecholamines, especially norepinephrine and epinephrine, resulting in increases in blood pressure (via α1 receptors) and heart rate (via β1 receptors). The pheochromocytoma was in the left adrenal gland and was identified by meta-iodobenzylguanidine (MIBG) imaging, which labels tissues that have norepinephrine transporters on their cell surface (see text). In addition, he had elevated plasma and urinary norepinephrine, epinephrine, and their metabolites, normetanephrine and metanephrine. The catecholamines made the blood pressure surge and the heart rate increase, producing a typical episode during the examination, perhaps set off in this case by external pressure as the physician palpated the abdomen. His profuse sweating was typical and partly due to α1 receptors, although the large magnitude of drenching sweats in pheochromocytoma has never been fully explained. Treatment would consist of preoperative pharmacologic control of blood pressure and normalization of blood volume if reduced, followed by surgical resection of the tumor. Control of blood pressure extremes might be necessary during surgery, probably with nitroprusside