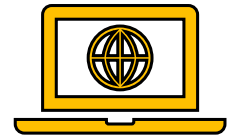
PC
Pharmacology Concepts
By Rajesh Choudhary

ANS Pharmacology



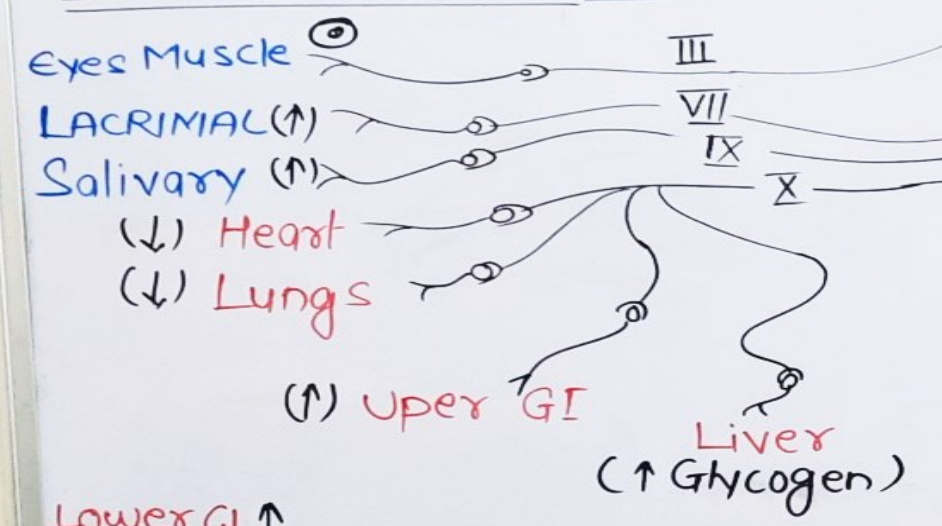
Website

Videos

Pharmacology 3 | U 3

AUTONOMIC NERVOUS SYSTEM

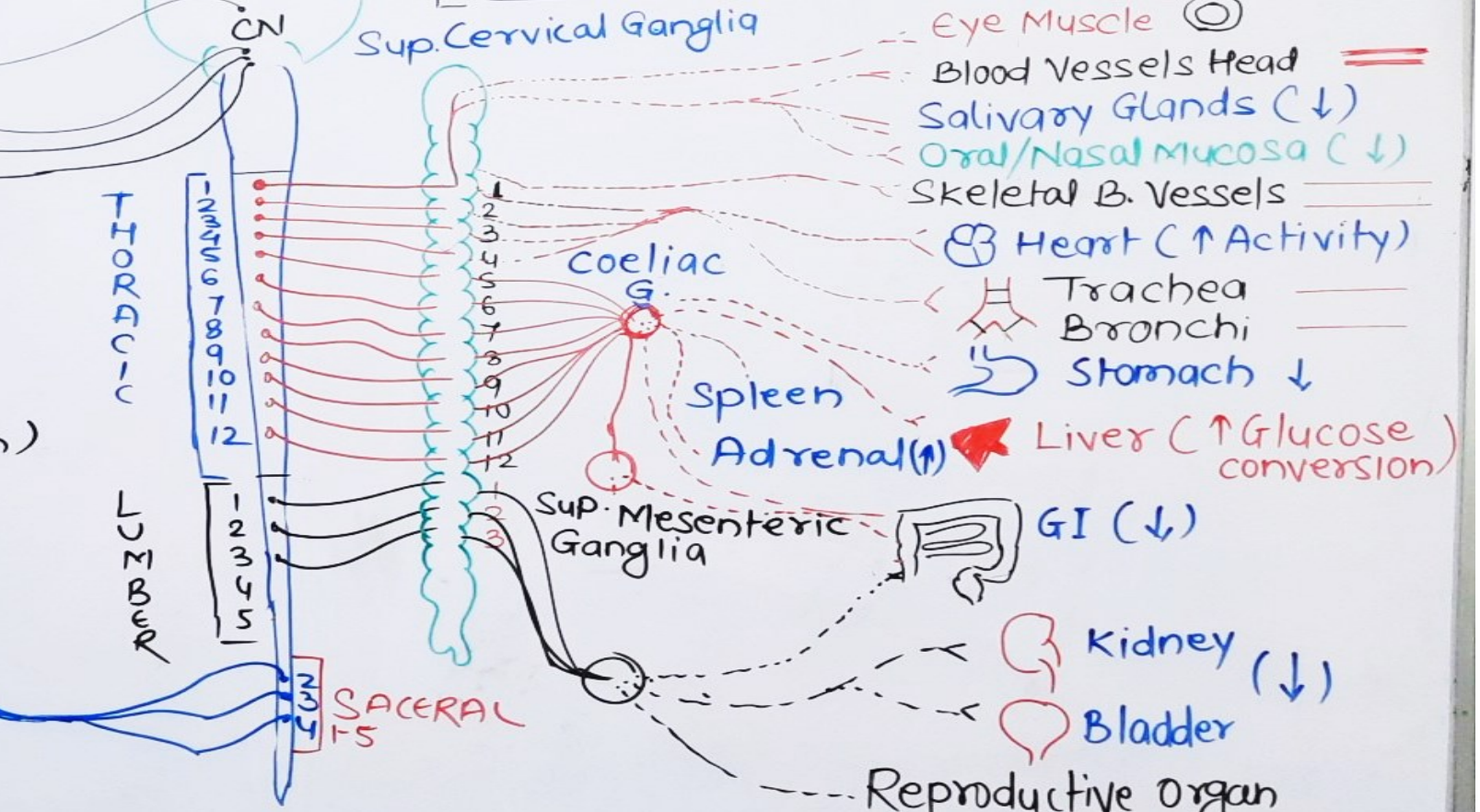
PARA SYMPATHETIC
[CRANIO-SACERAL | CHOLINERGIC]



"REST AND DIGEST"

"CONSERVE ENERGY"

SYMPATHETIC
[THORACO-LUMER | ADRENERGIC SYSTEM]

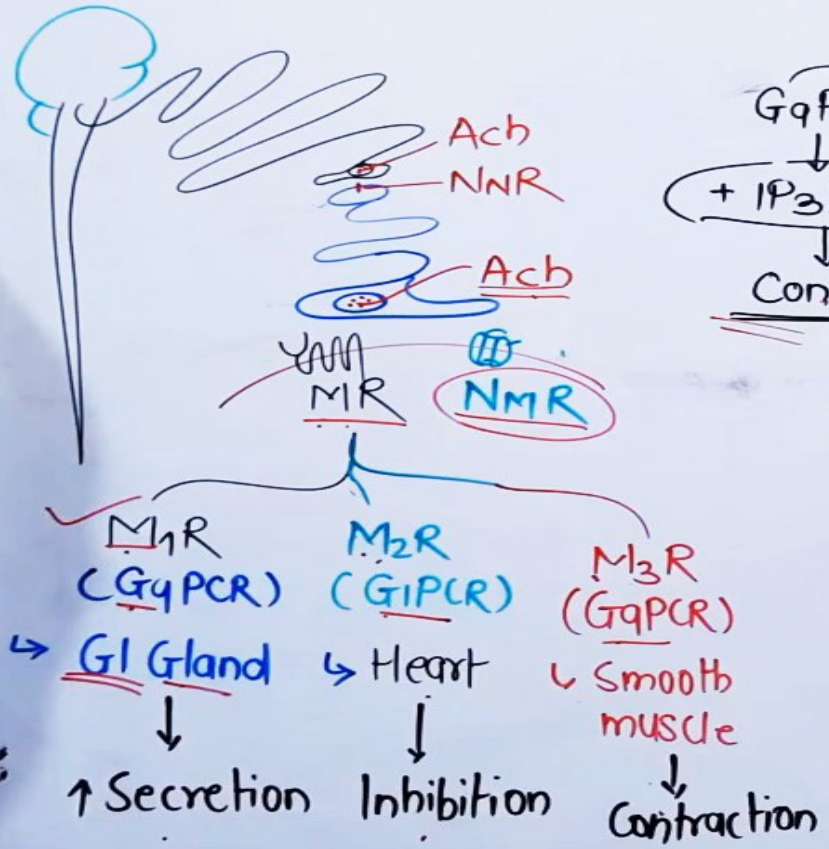


"3F = Flight, Fight & Fear"

"Expend Energy

AUTONOMIC NERVOUS SYSTEM

PARASYMPATHETIC SYSTEM



M_1R (G_qPCR) → GI Gland → ↑ Secretion

M_2R (G_iPCR) → Heart → Inhibition

M_3R (G_qPCR) → Smooth muscle → Contraction

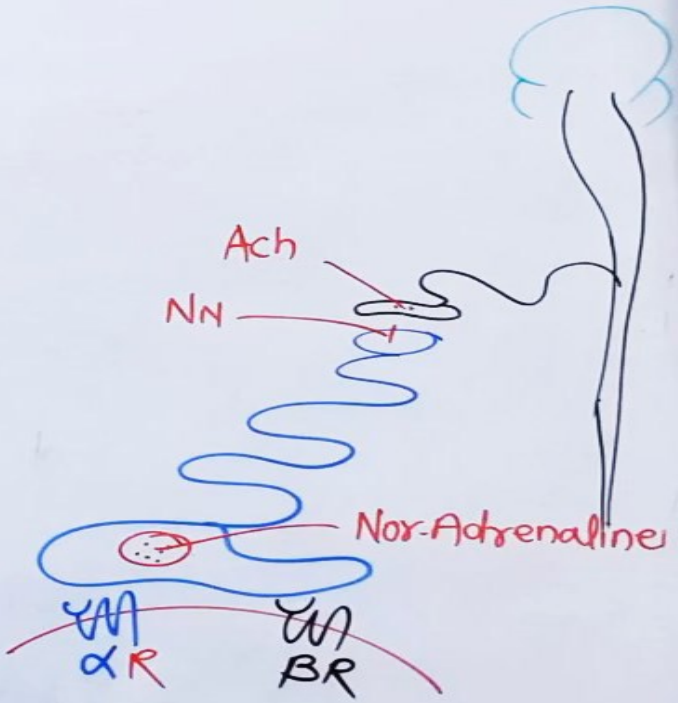
SYMPATHETIC SYSTEM

Receptors

- LGIC
- ELR
- NR → GPCR
  - G_qPCR → $+IP_3/DAG$ → Contraction
  - G_iPCR (−) cAMP (+) G_sPCR

cAMP → Cardiac muscle → Contraction (Gi (−), Gs (+))

cAMP → Smooth muscle → Relaxation (Gi (−), Gs (+))



αR
- α_1R (G_qPCR) → Smooth muscle → Contract
- α_2R (G_iPCR)

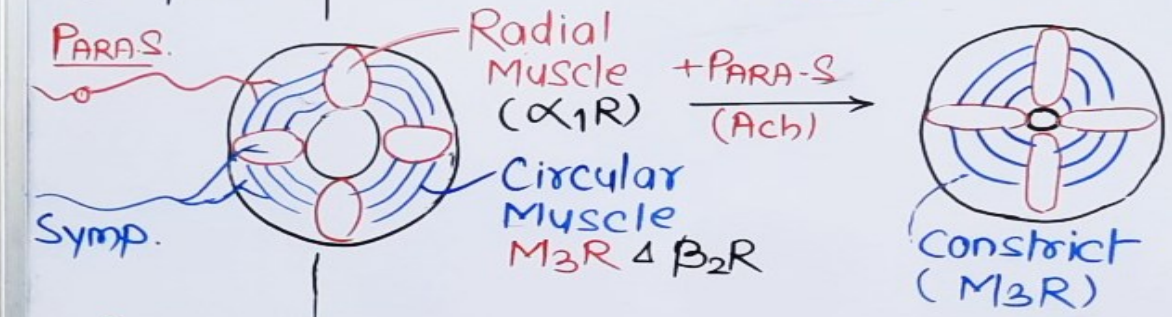
βR
- β_1R (G_sPCR) → Heart → Stimulation
- β_2R (G_sPCR) → Smooth mus → Relax
- β_3R (G_sPCR) → Fat cell → Lipolysis

AUTONOMIC NERVOUS SYSTEM

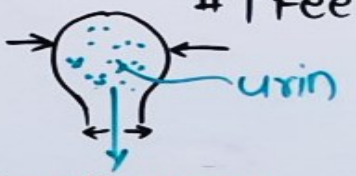
PARASYMPATHETIC SYSTEM

Ach → M_1R (G_q), M_2R (G_i), M_3R (G_q)

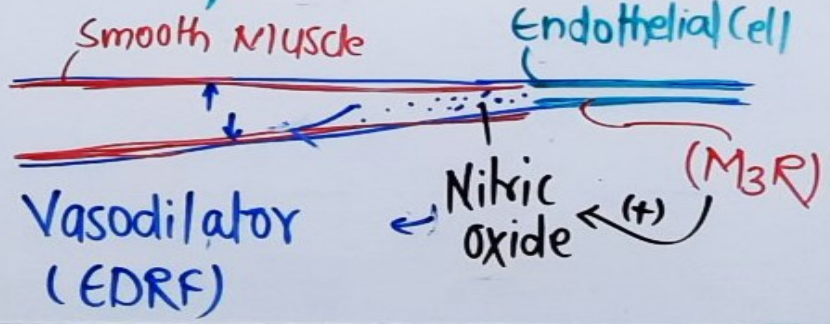
1. Eyes Mus. (Pupil)
   - # Constriction → Miosis
   - # Accomodate for "Near" Vision



2. Smooth Muscles
   - 1 Brochi – M_3R → Constriction
   - 2. GI muscles → M_3R – Constriction
   - 3. Urinary Bladder
     - # ↑ Feel of Urination



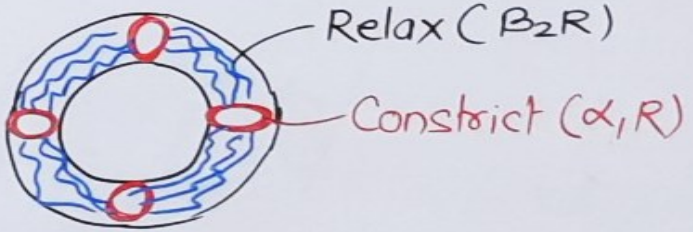
3. Blood vessels



SYMPATHETIC SYSTEM

Nor-Ad/Ad. – α_1R (G_q), βR (G_s)

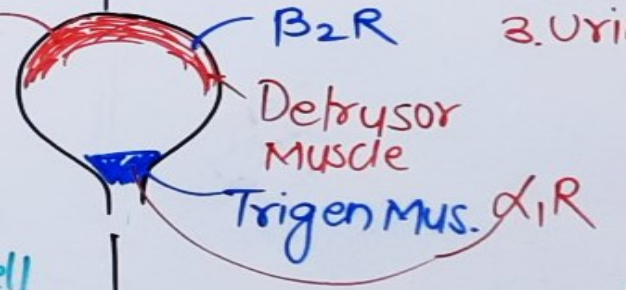
- # Dilitation → Mydriasis
- # Accomodate for "Far" Vision



Symp. Action → (Adr.) + α_1 & β_2

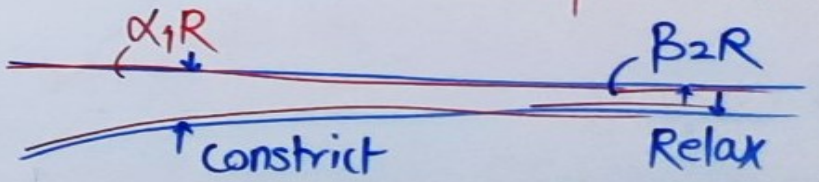
1 Bronchodilitation (B_2R)

2. GI Muscle – Relaxation



3. Urinary Bladder
   - # ↓ Feel of Urination

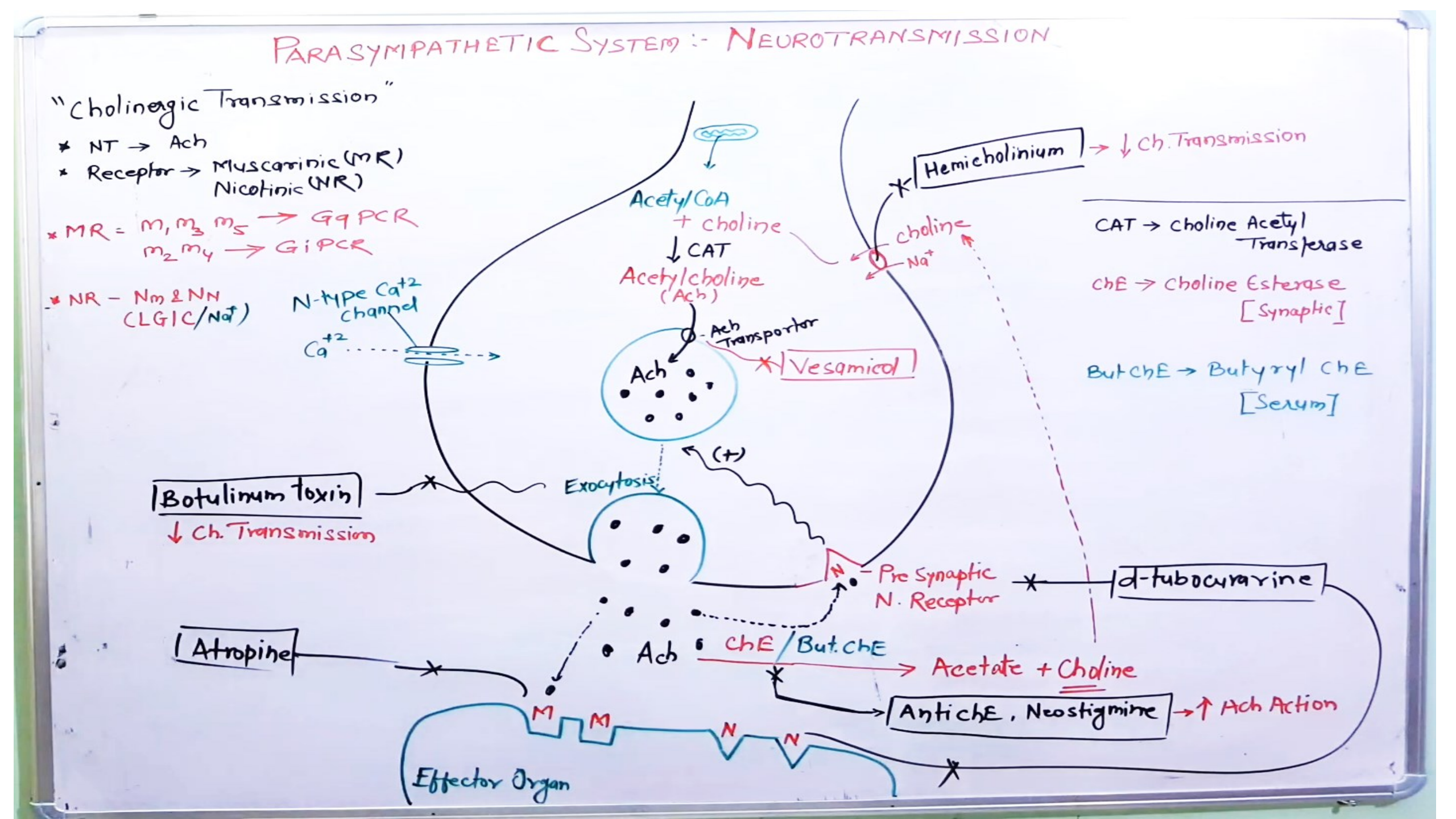
4. Uterus
   - # Normal → β_2 – Relax
   - # Labor pain → α_1 → Constriction



AUTONOMIC NERVOUS SYSTEM

	PARASYMPATHETIC SYSTEM Ach → M_1R (G_q), M_2R (G_i), M_3R (G_q)	SYMPATHETIC SYSTEM Nor-Ad/Ad. – α_1R (G_q). βR (G_s)
4. HEART	# M_2R (G_i) ↓Conduction → ↓HR (–chronotropic) ↓Force of contractn (–Inotropic)	# β_1R (G_sPCR) # ↑HR – (+chronotropic) # ↑FC – (+Inotropic)
5. Gland Secretn	– GI Secretion – (M_1R) – ↑ – Salivary – (M_3R) – ↑ → Nasal – (M_3R) – ↑ – Sweat – (M_3R) – ↑	# GI Secretn # Salivary## # Nasal / Mucus # Sweat – (M_3R) – ↑ – ↓
6 Metabolism	# Restoratn of metabolic Reserve # Eleminatn of waste	# Glycogenolysis (α_1 β_2) # Gluconeogenesis # Lipolysis (α_1, β_3R) → ↑Glucose – ↑Energy
7. Reproductive	# Erection	# Ejaculation

PARASYMPATHETIC SYSTEM :- NEUROTRANSMISSION

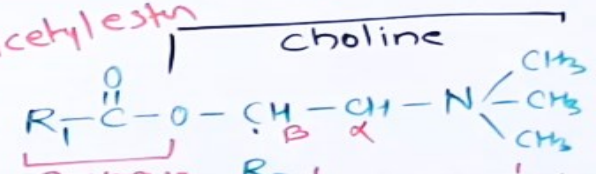


PARASYMPATHOMIMETICS : CLASSIFICATION OF DRUGS

I. Choline Esters

		R_1	R_2
A	- Acetylcholine	$-CH_3$	$-H$
M	- Methacholine	$-CH_3$	$-CH_3$
C	- Carbachol	$-NH_2$	$-H$
B	- Bethanechol	$-NH_2$	$-CH_3$

Acetylester



Carbamate esters (NH_2CO-)

↑ DIRECT ACTING CHOLINOMIMETICS

	ChE	MR*	NR*
* A -	++++	+++	+++
M -	+	++++	None
* C -	Negligible	++	+++
B -	Negligible	++	None

II Natural Alkaloids -

- → (+) Muscarine (Amanita muscaria)
- → Pilocarpine (Pilocarpus microphyllus) G
- → Arecholine (Areca catechu)
- → Nicotin, Leboline, Oxotremorine

III ChE Inhibitors / Anti-ChE [INDIRECT ACTING]

A. Carbamate Ester / Riversible

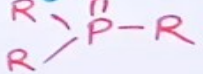
$R-O-\overset{O}{\overset{\|}{C}}-NR_2$

- → Physostigmine (Glucoma)
- → Neostigmine W
- → Pyridostigmine W — MG
- → Edrophonium
- → Rivastigmine L
- → Donepezil L
- → Tacrine (Acredine) L — AD

W = water soluble L = Lipid Soluble

B. Irriversible

- Carbomate → Carbaryl, Propoxure
- Organophosphates



- Isoflurophate
- Echothiophate — used in Glaucoma

- → Parathione
- Malathione — Insecticides

- Tabun
- Sarin
- Soman — Nerve Gases for warfare

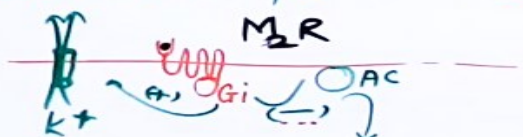
PARASYMPATHOMIMETICS : PHARMACOLOGY

Ach → M_1/M_3 → GqPCR → ↑ IP_3/DAG → Contraction
M_2 → GiPCR → ↓ cAMP Signaling → ↓ Cardiac Activity

General P'Cological Action :-

⇒ Muscarinic (MR) Action →

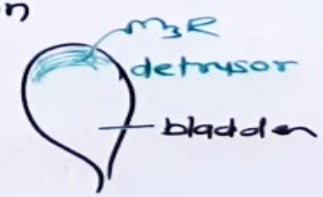
1. Heart (M_2R) → ↓ HR [-chronotropic] by ↓ in Automaticity / Pacemaker (SA Node) activity.
→ ↓ Force of contraction (-Inotropic)
→ ↓ Conduction Velocity (AV node) [-dronotropic]



Hyperpolarization → ↓ HR, ↓ Conduction
↓ cAMP → ↓ FC

2. Blood Vessels → Vasodilation by EDRF/NO → ↓BP
- At high dose → + A. ganglia → + Sympathetic → Vasoconstriction [↑BP]

3. Smooth mus. (M_3R) → "Constriction"
- GI
- Urinary bladder
- Bronchi



4. Eye/Pupil – Pupil constriction / "miosis" by circular mus. [M_3R] constriction. Accomodate for Near vision

→ used as anti-glaucoma drug (due to ciliary mus contract)

5. Gland Sec. → ↑ GI gland Secretion – M_1R
↑ other gland Sec. – M_3R

⇒ Nicotinic (NR) Action →
→ Skeletal mus. contraction (NmR)
→ Ganglionic Stimulation

Organoph. poisoning
Antidote -
Atropine
Pralidoxime
Diazepam
↓ ChE Reactivator

Side Effect/ADR → Bradycardia, Hypotension, Diarrhoea, Bronchospasm, Acidity,

Contraindication – Asthma, Ulcer, CVS disorders, Hyperthyrodism.

USE – Glaucoma – Physostigmine, Pilocarpine, Carbachol, Ecothiophate
Mysthenia Gravis → Neostigmine, Pyridostigmine, Edrophonium (↳ diagnosis)
Alzimer → Rivastigmine, Donepezil, Tacrine, Galantamine
Post operative Ilius → Bethanechol, Neo & Pyridostigmine
Atropine/Belladona, Phenothiazine poisoning - Physostigmine

CHOLINERGIC RECEPTOR :- MUSCARINIC RECEPTOR

RECEPTOR	SIGNALING	LOCATION	ACTION	AGONIST	ANTAGONIST
M_1R (Neuronal)	G_qPCR [$\uparrow IP_3/DAG$]	CNS GI & Pencreatic Glands	→ ↑ Cognitive functn → ↑ Secretion	Ach, Methacholine Carbachol, Bethanechol	Atropine, Pirenzepine, Dicyclomine
M_2R Cardiac	G_iPCR ↓cAMP & ↑ K^+ conductn	Heart ↓HR ↓FC ↓Conductn	(−)chronotopic (−)Inotopic (−)dromotropic	A, M, C, B	Gallamine Tripitamine
M_3R (Glandular)	G_qPCR	Exocrine Glands Smooth muscle (GI, Bronchi, bladder)	↑ Secretion Contraction	Ach Carbachol	Difenidol
M_4R AutoReceptor	G_iPCR	CNS	↓Cholinergic activity ↑Locomotion	Ach	Atropine
M_5R	G_qPCR	CNS (S. nigra) Salivary Gland	↑ dopamine Release Regulate Motor function ↓ ↑ Salivation	Ach	Atropine

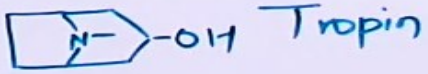
CHOLINERGIC RECEPTOR: NICOTINIC RECEPTOR

RECEPTOR	SIGNALING	LOCATION	ACTION	AGONIST	ANTAGONIST
N_N Nicotinic Neuronal 4 Subunit - transmem. 1 Subunit - wall α-8, α_2-α_9 β-3, β_2-β_4	LGIC/Na^+ - depolarization	Autonomic Ganglia $[(\alpha_3)_2(\beta_2)_3]$ Type III CNS - $[(\alpha_7)_5]$ Type I $[(\alpha_4)_2(\beta_2)_3]$ Type II Adrenal Medulla Pentameric ion pore	(+) Ganglia (+) low dose (-) high dose ↑ Adrenaline release ganglia N_N	Nicotine Acetylcholine Epibatidine CNS - ↑ Cognitive funct^n - Learning & Memory ↑ Locomotion ↑ body Temp ↑ Respiration modulate pain perception	Mechylamine Neurotoxine Hexamethonium
N_M Nicotinic muscular	LGIC/Na^+	Neuromuscular Junction $[(\alpha_1)_2 \beta_1 \delta \varepsilon]$	Skeletal muscles contraction Skeletal muscle N_M	Ach Carbachol Nicotine	d-Tubocurrarine "Curare Derivatives"

PARASYMPATHOLYTICS

* Anti-cholinergic/Antimuscarinic drugs
* These drugs oppose the action of Ach by blocking of MR not NR. Therefore, They are called Muscarinic blockers

CLASSIFICATION –



Tropin

I Natural Alkaloids
- Atropine (± Hyoscyamine) ← A. belladona
- Scopolamine (–/ℓ Hyoscine) ← H. niger
- +/d- Hyoscyamine
- Solanine ← Potato (Solanum tuberosum)

II Semisynthetic
- Homotropine – Used topically for Mydriasis
- Atropine methyl nitrate → used in abdominal colics, Acidity & Asthma

- Ipratropium
- Tiotropium
- Oxytropium

→ 4° Ammonium Analouge
→ used in "Asthma"
→ "Bronchiodilator"
→ M_3 Block

III Synthetic

(A) Mydriatics → Tropicamide, Cyclopentolate (M_3 block)

(B) Anti-Secretory & Antispasmodic – M_3 block

(i) 4° Ammonium – Peripheral Action
Propentheline, Oxyphenonium, Isopropamide, Glycopyrolate

(ii) 3° Ammonium – CNS, Eye,
Dicylomine, Pirenzepine

(C) Vasico-selective
Oxybutynine, Tolterodine

(D) Anti-Parkinsonian
Procyclidine, Trihexyphenidyl
Biperiden

OTHERS – TCAs, Phenothiazenes, Anti Histaminics

PARASYMPATHOLYTICS

PHARMACOLOGY OF ATROPINE

ATROPINE ⊿ Ach

↳ Oppose the Action of Ach
↳ Muscarinic Receptor Antagonist

1 CNS :- (+) Action
↳ Stimulate medullary centre (Vegal, Respiratory ⊿ Vasomotor)
↳ ↓ Vestibular Excitation (helps in motion sickness/ Antiemitic effect)
↳ ↓ Parkinson like effect (↓ Tremor & Rigidity)

2. Heart → ↑ Heart Rate / *Tachycardia [M_2R block]

3. Eyes :→ - Mydriasis (Pupil dilitation)
(M_3R block) - *Cycloplegia (paralysis of cilliary muscles)
- *Abolish light Reflection → "*Blurred near vision"
(M_3R block)

4 Smooth muscles → Relax all Smooth muscle
*GI, Bronchi, Eye, Bladder

5. Gland Secretion :- ↓ Glandular Secretion
GI, *Salivery, *Sweat, Bronchial

ADR* :- Belladonna Poisoning

* Tachycardia, * Blurred vision, * GI-Constipation,
* Dry mouth, * Hot Skin * Photophobia,
* Psychotic behavior, * Delirium

Diagnosis - methacholine (5mg) or Neostigmine (1 mg) administration fails to produce muscarinic actio

Treatment → "Physostigmine (1-3 mg IV/sc)"

CLINICAL USES -

1. Antisecretory as a Preanesthetic → Glycopyrrolate
2. Antispasmodic (Abd. Cramp) - Hyoscine Butyl bromide
3. Antiasthmatics - Ipratropium, Tiotropium
4. Antiemetic/motion sickness - Scopolamine ⊿ Dicyclomine
5. Mydriatics/Cycloplegic - Tropicamide Cyclopentolate
6. Antiulcer → Pirenzepine ⊿ Dicyclomine
7. Organophosphorus/ Mushroom poisoning - Atropine

CONTRA-INDICATION → Arrhythmia
Glaucoma

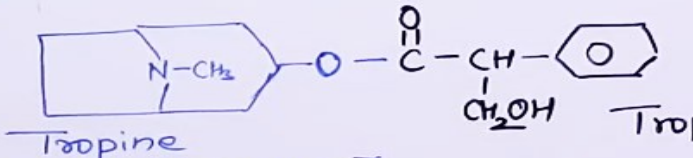
ATROPINE & SCOPOLAMINE

ATROPINE

Source - 'Atropa belladona", Solanacea family

↳ (±) Hyoscymine - Racemic mixture

↳ Ester of Tropine & Tropic acid



Tropine

[3-hydroxy Tropane]

Tropic acid

Main Action on → Heart, Bronchi, GI muscle

↳ It has Lower Activity & Potency

↳ CNS Effects - minimal

* main Use - Organophosphorous poisoning,
Bronchodilatn
GI (Abdominal) Cramp

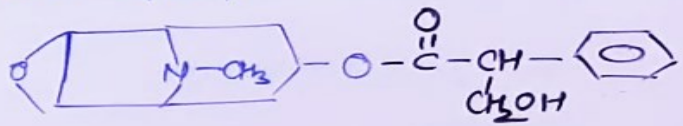
Atropine poisoning → Physostigmine

SCOPOLAMINE

Source → "Hyoscyamus niger", Solanacea

↳ (-) Hyoscine - levo forme, more active

↳ Ester of epoxy derv. of Tropine & Tropic Acid



main Action on - Eye, Exocrine Glands, "CNS"

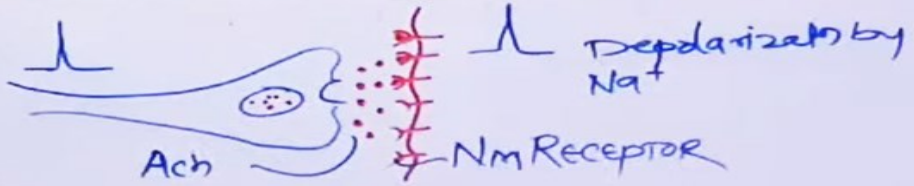
Atropine < Scopolamine, It has higher activity & Potency

- CNS Effects - "Marked" - Cross the BBB
↳ CNS Deprassant-effect

* main Use - Antiemetic / Motion Sickness
Anti-Scretory
"NARCO TEST" - For Amnesia effect
(memory loss)

Scopolamine poisoning → Bethenachol

SKELETAL MUSCLE RELAXANT



Neuromuscular Blockers :- structural analauge of Ach & act either as Antagonist (Non-Depolarizing agent) or Agonist (Depolarizing agents)

Ⓐ Non-Depolarizing (Competitive) Blocker
↳ D-tubocurarin, Atracuronium, Pancuronium, Vencuronium

* Their action is reversed by Anti-chE
* Prevent the depolarization of skeletal muscles by blocking Nm Receptors
* At High dose :→ Block Na^+ channel & ↓ Neurotransmission
→ Muscular paralysis - face, Eye, Finger, Limb, Neck, trunk, Ribs & Diaphragm

B. Depolarizing Agents - Agonist
Succinylcholine, Decamethonium
↳ ↑ duration of channel openig
Phase I - Depolarization - Muscles Twitching
Phase II - Contineous depolarizing fails to transmit further impulse - Flacid paralysed

Effects :- Post operative mus. pain
- Hyperkalemia
- ↑ IOP
- Produce malignant Hyperthermia

CENTRAL MUSCLE RELAXANTS

Mefenesin - Anti-dote for Strychnine poisoning

Baclofen - $GABA_B$ Agonist - GiPCR

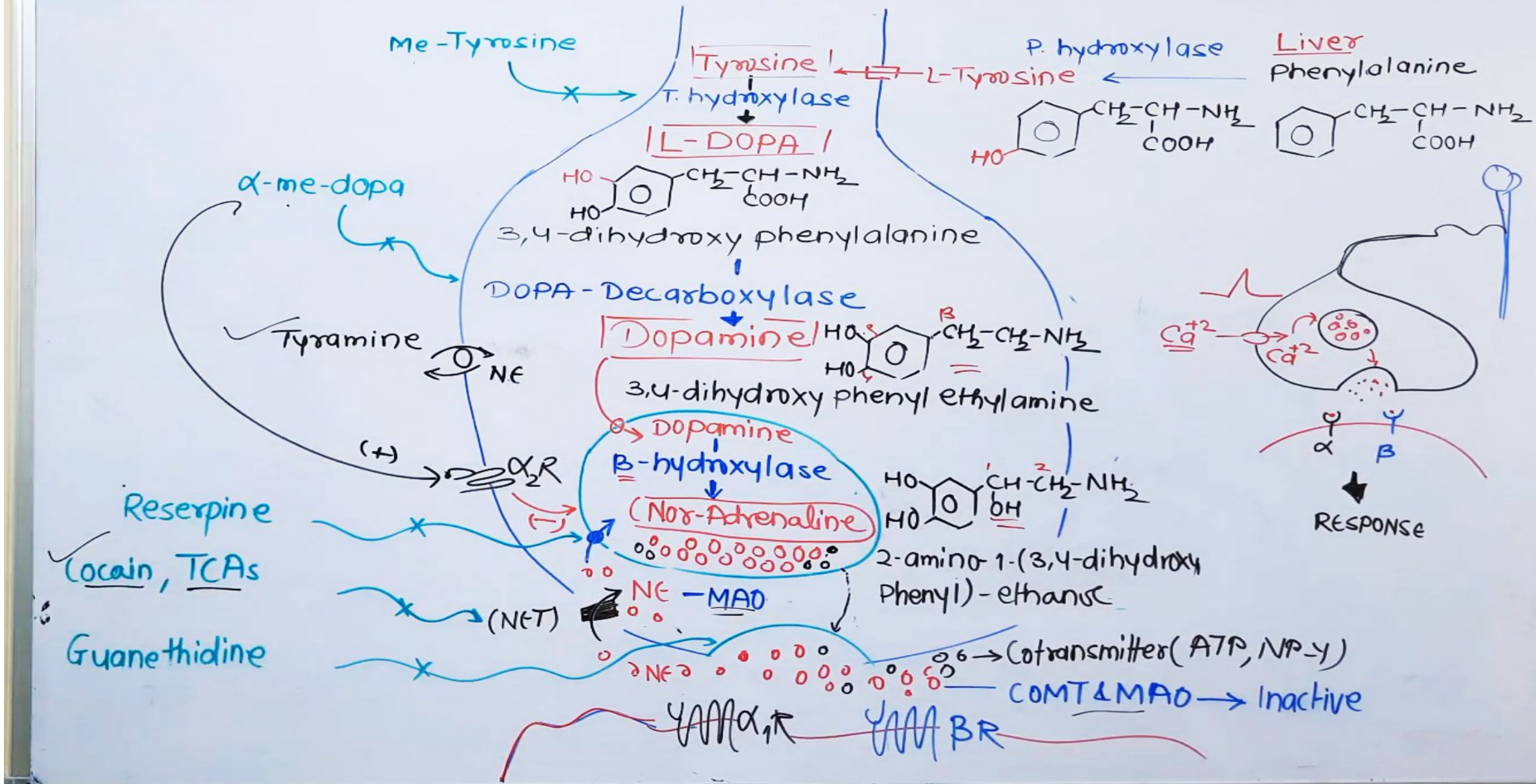
Dentrolene - ↓ Ca^{+2} release From SR by blocking RyR

Diazepam - $GABA_A$ R

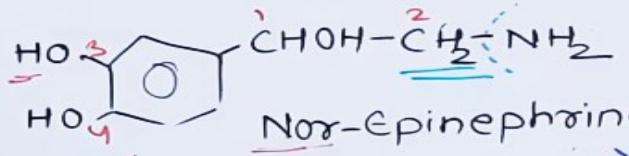
Meprobamate - Barbiturate like action

ADRENERGIC NEUROTRANSMISSION AND BIOSYNTHESIS

Biosynthesis :- Proposed by "Blaschko" in 1989. (Adrenergic & Dopaminergic Neuron)



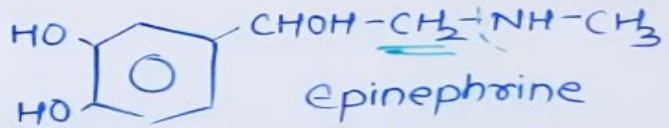
METABOLISM OF ADRENALINE AND NOR-ADRENALINE



Nor-Epinephrine

(Mono-Amino Oxidase)

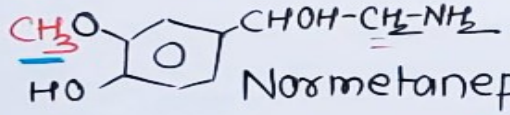
MAO



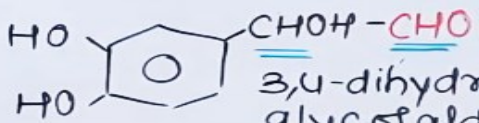
Epinephrine

COMT

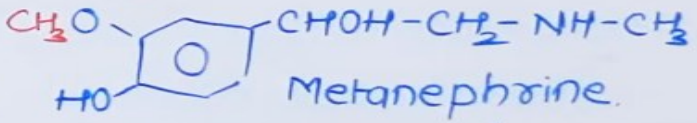
COMT (catechol-O-me-transferase)



Normetanephrine



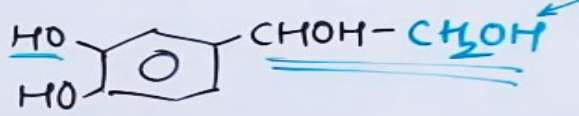
3,4-dihydroxy phenyl glycolaldehyde



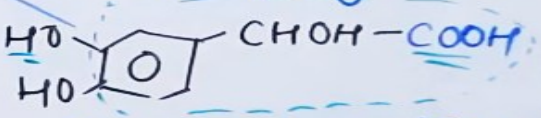
Metanephrine

Ald Reductase

Ald Dehydrogenase

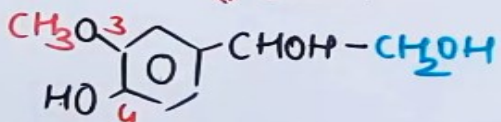


3,4-dihydroxyphenyl ethyleneglycol

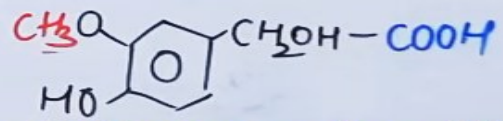


3,4-dihydroxy Mandelic acid

COMT



4-hydroxy-3-methoxy phenyl ethyleneglycol

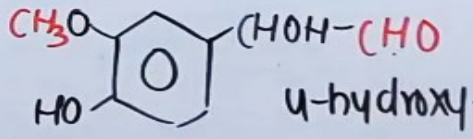


4-hydroxy-3-methoxy-Mandelic acid

(Vanillylmandelic acid)

Ald Reductase

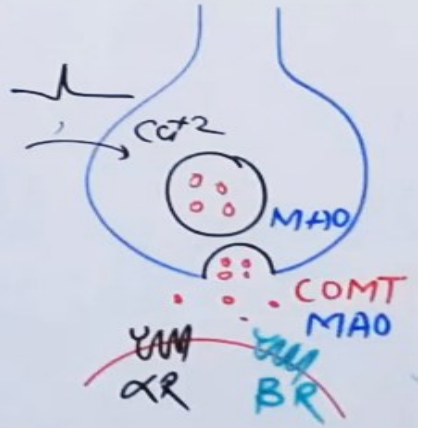
Ald Dehydrogenase



4-hydroxy-3-methoxy phenyl glycolaldehyde

MAO

MAO



ADRENO-RECEPTOR: α-RECEPTOR UPDATES

History - In 1896, Oliver & Schafer ⇒ Adrenal gland extract cause the rise in arterial Pressure (BP), following in 1913, Dale - isolated adrenaline causes two different effects on different area - Vasoconstriction & Vasodilation.
And In 1948, Ahlquist - Classified Adrenoreceptor into two category → [β - (β1, β2, & β3) - GsPCR; α - [α1 - α1A, α1B, α1C, α1D - GqPCR; α2 - α2A α2B α2C - GiPCR, GqPCR]]

α_{1A}

Locatⁿ - ① CNS - Excitation, NT Release - Ach, Gly.
② Smooth mus. → Constriction
Vessels - ↑ BP
Bladder - ↓ urination
Eye Radial mus - Mydriasis
Uterus → Baby delivery
GI muscle - Relax [by NO, P_2Y, Peptide Recep.]
③ Salivery Glands - Secretion

α_{1B}

- Spinal cord
- Liver - Glycogenolysis & Gluconeogenesis

α_{1D}

- Aorta
- Femoral artery

All α_1 → GqPCR
(+) IP_3/DAG
(+) ERK/MAPK

Other functⁿ - 1. Atention & Memory - ⊕ Glutaminergic Trans.
2. ↑ Locomotion → (+) Dopaminergic neuron at S. nigra
3. multipk Sys. Atropy - α_{1B}-overexpressed in Neurodeg. Dis. like PD, Cerebral Atoxia,

→ Order of Catecholamines - NA ≥ Ad

Agonist - Phenylephrene, methoxamine

Antagonist - "Zosin" - Prazosin, Terazosin, Doxazosin

α_2 (↓ cAMP Pathway)

1. Pre junction of nerve ending → ↓ NE Release (Coronary artery, CNS artery, Pencreatic vess.)
2. Hetero-receptor → Cholinergic (ileum) → ↓ Ach
→ SHT (brain) - ↓ SHT
3. B. Vessels - (α_{2A}) Presynaptic - GiPCR, Post Synaptic - GqPCR
4. Pencreatic β-Cell - ↓ Insulin Secretion
5. Platelets - Aggregation

Ad > NA

Agonist → Clonidine, α-me dopa - Antihypertensive in pregnancy, Oxymetazoline

Antagonist → Yohimbine, Idazoxan, Rauwolscine

ADRENO-RECEPTOR: β-RECEPTOR UPDATES

β_1R

(a) Heart - (+) Inotropic (FC)
(+) Chronotropic (HR)

GsPCR → cAMP/PKA

(+) Inotropic ← ↑ Ca^{+2}_i ← ↑ TP^H ← (+) NHERF

(+) Chrono. ← (+) Pacemaker

(b) Salivary Glands → Amylase secretion

(c) JG cells of kidney → Renin secretion

Order → Iso > Ad ≥ NA

Agonist - Dobutamine
Xamoterol

Antagonist - Atenolol
"lol" Metaprolol
Bisprolol
Esmolol

β_2R

(a) Smooth muscles
(+) Lucitropic effect

cAMP/PKA → (-) MLCK → Relaxant effect
cAMP/PKA → (+) phospholamban

↳ B.V., Bronchi, Uterus, Eye (circular mus), Bladder

(b) Heart → + Ino & chronotropic #
(c) Skelatal mus → contraction #
#ADR - Tachycardia & Tremor

d) Liver - Glycogenolysis ← Sk. mus
e) Ad.-nerve ending → ↑ Ad/NE Release
F) Mastcell - ↓ Histamine Release

Order - Iso ≥ Ad

Agonist - Salbutamol, Terbutaline
Ritodrine

Antagonist - Butoxamine

β_3

a) Fats → Lipolysis & Thermogenesis

B) Skeletal mus - Thermogenesis

Iso ≥ Ad > NE

Agonist - BRL 37344
CGP 1217

Antagonist - Bupronolol

SYMPATHOMIMETICS / ADRENERGIC DRUGS

RECEPTORS — "Ahlquist", 1948

Adrenoreceptor (GPCR)
- β – [β_1, β_2, β_3] – GsPCR
- α
  - α_1 [α_{1A}, α_{1B}, α_{1C}, α_{1D}] – Gq
  - α_2 [α_{2A}, α_{2B}, α_{2C}]
    - α_{2A} → Gi
    - α_{2B} → Gq

CLASSIFICATION

I. Based on Action

(A) Direct Acting – "Agonist"

P D SAT at the DINER

Phenylephrine (α), Dobutamine – ($\beta_1 \gg\gg \alpha$)

Salbutamol, Albuterol, Terbutaline – $\beta_2 \gg \beta_1$

Dopamine – (α_1, β_2, D_1), Isoprinaline (β)

Nor-Epinephrine (α, β_1, β_3), Epinephrine (α & β)

Ritodrine (β_2)

⇒ Only α → Phenylephrine – $\alpha_1 \gg\gg \alpha_2$

= Only β – Salbutamol, Albuterol, Terbutaline – $\beta_2 \gg\gg \beta_1$

Isoprinaline (β_1 & β_2), Ritodrine β_2 (uterus)

⇒ Both = "By D-END have both"

α & β Dopamine, Epi, Nor-Ep, Dobutamine

(B) Indirect Acting – ↑ Synthesis & release of NE/Ep

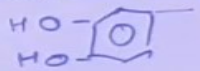
Tyramine, Amphetamine, Cocain, Ephedrine

(C) Mixed Acting – (+) Receptors & ↑ Syn or Release

Ephedrine, Amphetamine, Mephentamine

II. Based on structure –

(A) Catecholamines – NE, Ep, Iso, Dopamine (DA), Dobutamine (Dob)



II Based on Therapeutic Uses –

(A) Cardiac stimulant – Ad, Iso, DA, Dobutamine* (β_1)

B) Pressure Agent – Ex-PEND your BP = ↑BP → (α_1)

↳ Ep, Phenylephrine, Ephedrine, NE, DA

C) Bronchodilators β_2 → "SAT", Fometerol

D) CNS stimulant – DA, Amphetamine

E) Nasal Decongesant (α_1) – Xylometazoline, Oxymetazoline, Nephazoline

(F) Uterine Relaxant – Ritodrine, Isoxuprine

(G) – Appetite Supressant – Sibutramine, Fenfluramine

SYMPATHOMIMETICS / PHARMACOLOGY OF ADRENALINE

Adrenaline → [(+) βR – GsPCR; (+) α_1R – GqPCR]

Adrenaric System activates in "Emergency" Condition – 3F – "Fight, Flight & Fright"

PHARMACOLICAL ACTIONS :–

1. HEART – (+) B_1R → ↑HR (+Inotropic)
   → ↑Force of contraction (+chronotropic)
   → ↑Cardiac Output & ↑O_2 Consumption

2. B.P. / B.Vesseles – α_1 – Constriction → ↑BP
   β_2 – Relaxation → ↓BP

   α_1 → mucous mem., Renal bed, Cuteneous
   β_2 → Coronary artery, Sk.mus. & Liver

NE – α_1 → ↑SBP/DBP — ↓HR [Vegal Action]
↑↑ mean BP
Reflex Bradycardia due to Ach

Ep → ↑SBP(α_1) / ↓DBP(β_2) → ↑ mean BP
HR → ↑(B_1R) & ↓ Vegal Action

Iso → ↑SBP (B_1) / ↓↓DBP (β_2) = ↓ mean BP
HR → ↑ B_1 & Reflux Tachycardia (↓Ach)

3 RESPIRATION – Bronchodilation (β_2)
+ Resp. centre

4. Eyes → Mydriasis (↑ Pupil size)
   α_1 – Radial mus – constrict → ↓Aq. Secretion
   β_2 – Circular mus. – Relax ⇒ ↑ Aq. Secretion

5. Smooth muscles – GI – Relax
   → Bladder → Detrusor (β_2) (Relax)
   Trigen (α_1) → constrict ⇓ urination
   → Uterus
   α_1 – Constrict
   β_2 – Relax – In normal day

6. Sk. muscle – Contraction – (β_2)

7. CNS – (+), Alertness, Restlessness, Tremor
   * Loss of Biogenic Amine [5HT & NE] Causes Depression

8. Metabolism :– Glycogenolysis [α_1, β_2],
   Lipolysis (β_3), Calirogenesis (β_1 & β_2)
   Hyperglycemia

ADR ⇒ * Ventricular Tachycardia
* Pulmonary Oedema, * Cerebral Haemorage,
* Tremor, Restlessness

USE – Shock, Hypotension

CONTRAINDICATION – CVS disorder – HTN, Angina, Arrhythmia
– Hyperthyrodism

SYMPATHOLYTICS :- ADRENOCEPTOR BLOCKERS

→ Block the action of sympathetic system by Antagonising the α & β receptors

I. α-blockers

(A) Non-Selective → α_1 & α_2

Phenoxybenzene (I), Phentolamine
Tolazoline, Dihydro ergotamine Δ
Dihydro ergotoxine

(B) α_1-blockers – Antihypertensive

Prazosin, Terazosin, Doxazosin → ↓BP

Alfuzosin, Silodosin, Tamsulosin – ↓BPH

(C) α_2-Blockers –

Yohimbin & Rauwolscine

II Non-Selective Adreno-blockers – α + β

Labetalol, Carvedilol
Cartelol, Bucindolol] 3rd Gen

III β-blockers

A) Non-Selective ($B_1 + B_2$) – 1st Gen

Propranolol — Nadolol
Pindolol → (ISA) — Penbutolol
Timolol

(B) Selective B_1 blocker

New β-Blocker Acting Exclusively At myo Cardium

3rd Gen: Nebivolol, Betaxolol
2nd Gen: Bisprolol, Acebutolol (ISA)
Esmolol (ISA), Atetenolo, Metoprolol (2nd Gen), Celiprolol (3rd Gen)

(C) Selective B_2 Blocker – Butoxamine

CVS

B_2 → ↓BP,
B_1 → ↑ HR & FC
α_1 → ↑ BP

1) α_1 blocker + Ad. → ↓↓ BP, ↑↑ HR

2) β blocker + Ad → ↑BP, ↓HR (↳ Acute) | ↓BP ↓HR (↳ Chronic)

3) B_1 blocker + Ad → ↑↓ BP, ↓HR

PHARMACOLOGY OF α-BLOCKERS

I α_1-Blocking Action:- (Phenoxybenzene)

1. CVS ⇒ ↓TPR (Total Peripheral Resistance)
   ↓↓ BP Δ ↑↑HR (Tachycardia)*

   BP = CO x TPR | CO = HR x SV

* Vasomotor Reversible action of Dale:-
  α_1-blocking causes fall in BP by abolish the action of Ad. on α_1 receptors, Δ dominant action on β_2 receptor

2. Kidney → marked Hypotension causes ↓ in GFR resulted in Na^+/water retain tion*
   by RAS activation [β_1 activation by Ad] (↑)

3. Other Effects:-
   Eyes → Miosis* (pupil constriction)
   Nassal → stiffness*
   GIT → ↑ GI motility (diarrhoea)*
   Bladder tone → Relax (↑ urination)
   ↳ ↓ Prostate Resistance to urination
   Vas-deference → ↓ Semen Ejaculation*

ADR/Side Effects

→ Reflux Tachycardia → Diarrhoea
→ Peripheral Edema → Sexual dysfunction
→ disturbe in far vesion → Nassal stiffness
⇒ Postural Hypotension

Clinical uses –

↳ Hypertensive Emergency = "Zosins"
↳ Benign Prostate Hypertrophy (BPH) – Alfuzosin, Silodosin, Tamsulosin

↳ Pheochromocytoma
↳ Secondry Shock
→ migrane → Ergot Alk. = Ergotoxin Δ Ergotamine

II α_2-Blocking Action

→ Vasoconstriction, ↑ NA release, ↑ Insulin release

Ergot Alk → (A) Amino Acid Alk = Ergotamine Δ Ergotoxin
(B) Amine Alk = Ergometrine
↳ No α_1 activity

α_1 blocking Action → DH Ergotamine > DH Ergotoxin
Vasoconstrict → Ergotoxin > Ergotamine

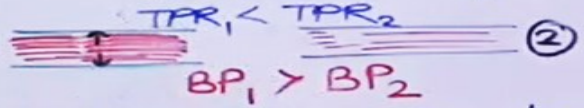
* DH Ergotamine ⇒ Cognitive Enhancer

PHARMACOLOGY OF B-BLOCKERS / PROPRANOLOL

A. Heart:- ↓HR (−chronotropic), ↓FC (−Inotropic) (−B_1R) ↓CO, ⇓Cardiac workload & O_2 demand *#

B. B. Vessels → ↓coronary blood flow & ↑TPR (−B_2R) in acute treatment [↑BP]

* During prolong therapy, ↓BP* is reduced by
↳ Vascular Adaptation



BP = ⇓CO × TPR↑
CO = ↓HR × SV↓

↳ ↓ NA △ Renin Secretion by B_1R blockade

C. Respiratory Tract : Bronchoconstriction *
(−B_2R) ↳ Asthmatic precipitation

D. Metabolism – ↓ Lipolysis → ↑ Fatty A, TG, LDL *
(−B_2) ↓ Gluconeogenesis △ ↓ Glycogenolysis *
↳ ↓ Carbohydrate Tolerance

E. Sk. Mus – ↓ muscular tone, ↓ Tremor *#, *
(−B_2) ↓ Exercise Capecity → ⇓ Blood flow
↓ Glycogenolysis

F. Eye – ↓ IOP, Aq. Secretion #
(−B_2)

G Uterus – Contraction *
(−B_2)

H. - CNS – Anxiolytic effect by *
Peripheral Action

I. Local Anaesthic effect, but not useful due to irritation.

P'kinetic – First Pass metabolism – ↓BA P : oral 40 : 1
Cross BBB, 90% PB,
Excrete through Glucoronic conjugation

* ADR = Bradycardia, Bronchocostriction, metabolic Disorder, Fatigue Sexual Impairment

C.I. – Asthma, Hyperlipidemic Patient

* Clinical uses → HTN, Angina, MI, Arrhythmia
↳ Anxiety, △ Tremor
↳ Migrane – Block catecholamine induce cerebral Vasodilation effect
↳ Glaucoma – Timilol (topically)

Drug Interactions :–
+ Digitalis → Cardiac Arrest
+ Verapamil → —!——
+ Oral Hypoglycemics → ↑↑ Hyperglycemia effect
+ α_1 Agonist ⇒ ↑↑ BP (Hypertension)