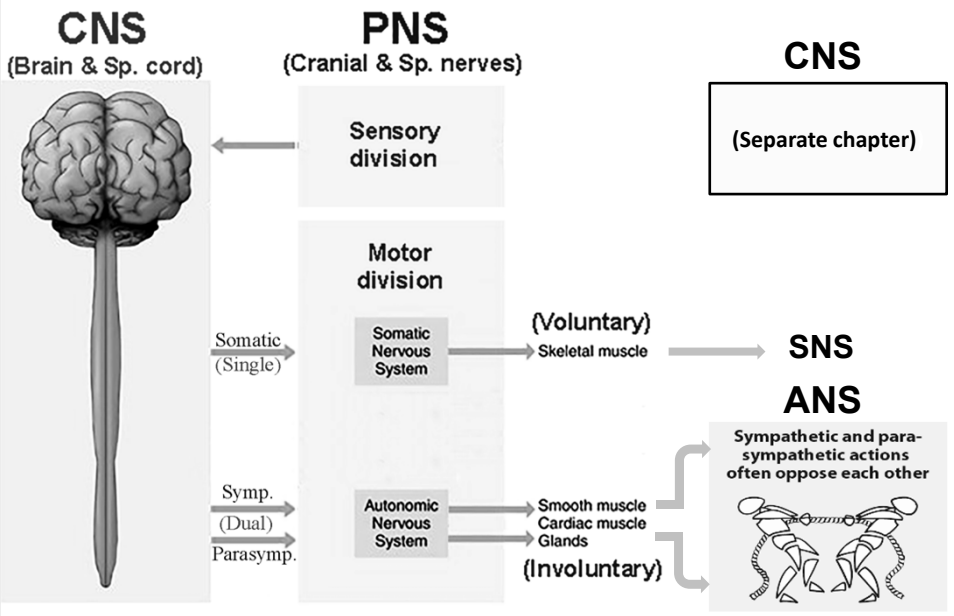
NERVOUS SYSTEM (PHAMACOLOGY)



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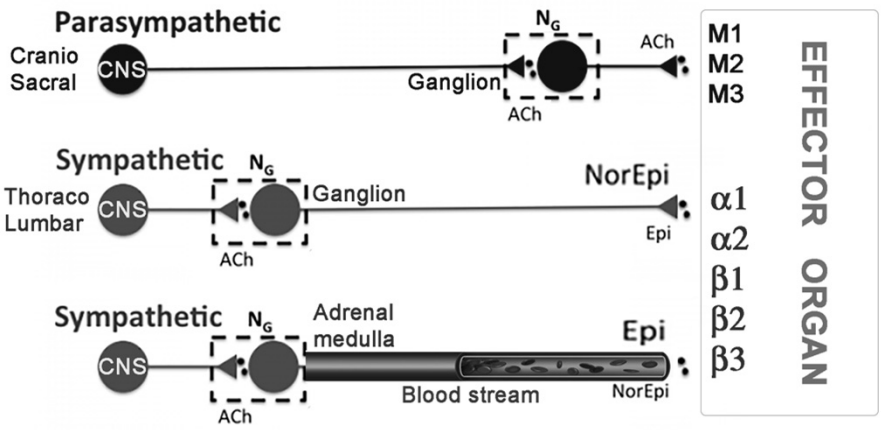
Symp. *vs* Parasym. nerves

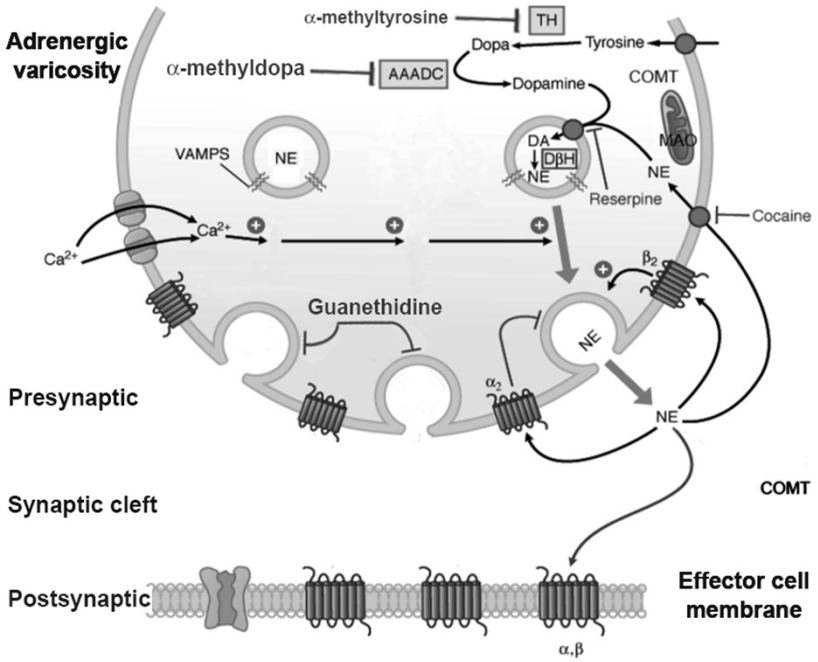


A DRUG can act *via*:

- CNS (centers),
- Ganglia (non-specific),
- Neuron (neuronal events),
- Receptor (receptor events).

2

SYMPATHETIC DIVISION



3

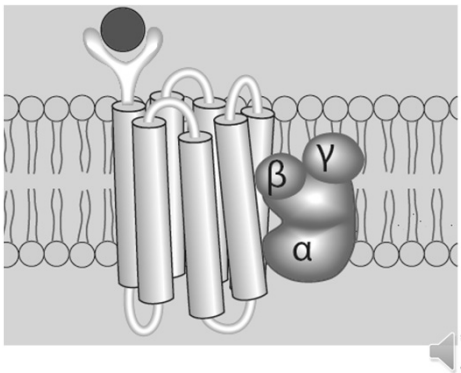
ADRENERGIC RECEPTORS

Def. : Adrenoceptors are membrane-bound receptors coupled with G proteins, specific to adrenaline, noradrenaline & their antagonists.

Location: - CNS (central),
- Nerve endings (presynaptic),
- Effector organs (postsynaptic).

Types:

- **Alpha (α):**
  - α_1
  - α_2
- **Beta (β):**
  - β_1
  - β_2
  - β_3



4

ADRENERGIC RECEPTORS

α1 receptor

Sites: Mainly effector organs (postsynaptic).

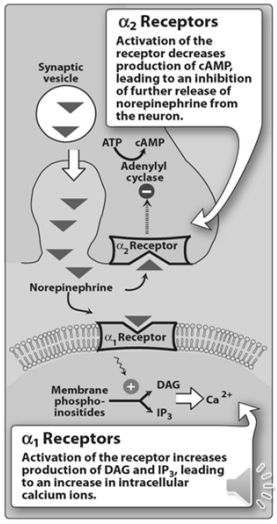
Mechanism: G_q-Protein → ↑PLC→ ↑IP_3 & DAG →↑Ca^{++} →response

Actions: (Fight and fright)

- Contraction of pilomotor muscle → erection of hair
- Contraction of dilator pupilae muscle → active mydriasis
- Generalized vasoconstriction → ↑ TPR → ↑Bl. Pr.
- Viscid salivation
- Spasm in sphincters of GIT and UB
- Ejaculation & contraction of prostatic capsule
- Contraction of pregnant uterus

Selective agonist: phenylephrine

Selective antagonist: prazosin



5

ADRENERGIC RECEPTORS

α2 receptor

Sites: Central; presynaptic; postsynaptic.

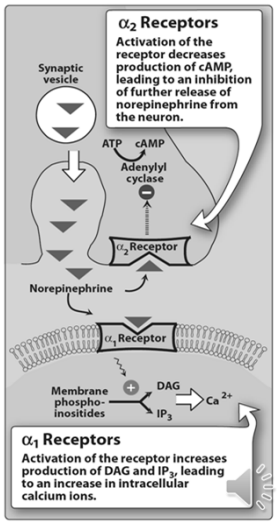
Mechanism: G_i-Protein → ↓AC→↓cAMP → ↓Ca^{++} →response

Actions: (Calming)

- ↓CNS → sedation & ↓ sympathetic centers.
- Presynaptic:
  - ↓release of NA
  - ↓ACH in enteric ganglia → relaxation of GIT
- Kidney: ↓release of renin → ↓ Bl. Pr.
- Pancreas: ↓release of insulin
- Adipose tissue: ↓lipolysis → ↓ Bl. F.F.A.

Selective agonist: clonidine

Selective antagonist: yohimbine



6

ADRENERGIC RECEPTORS

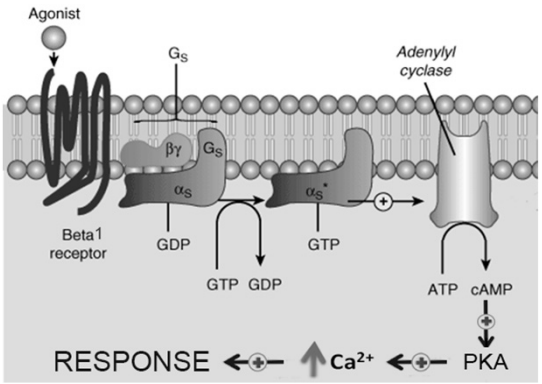
β1 receptor

Sites: Central; postsynaptic.

Mechanism: G_s-Protein → ↑AC→ ↑ cAMP → Protein kinase-A + open Calcium Channel → ↑ Ca^{++} → ↑response

Actions: (Alertness)

- ↑CNS → anxiety
- ↑heart →↑Cardiac output
- Kidney: ↑renin
- Adipose tissue: ↑lipolysis



Selective agonist: dobutamine
Selective antagonist: atenolol

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ADRENERGIC RECEPTORS

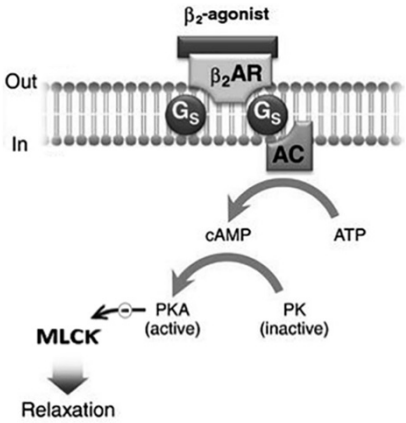
β2 receptor

Sites: Central; presynaptic; postsynaptic.

Mechanism: G_s-Protein → ↑AC→ ↑ cAMP →↓Myosin light chain kinase in SM. muscle, Bl.Vs, Bronchi, UB, Uterus → relaxation

Actions: (For muscle)

- Generalized VD especially for Sk. muscles
- Bronchodilation
- Uterus, UB & GIT walls: relaxation
- ↑glycogenolysis in liver & Sk. Muscles
- ↑release of insulin



Selective agonist: salbutamol
Selective antagonist: butoxamine

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ADRENERGIC RECEPTORS

β_3 receptor

Sites: Postsynaptic, mainly in adipose tissue.

Mechanism: G_s-Protein → ↑AC→ ↑ cAMP

Actions: (For catabolism)

-↑lipolysis

-↑thermogenesis

Selective agonist: octopamine

Selective antagonist: ---

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CLASSIFICATION OF SYMPATHETIC DRUGS

SYMPATHOMIMETICS
(drugs which stimulate adrenergic receptors & neurons and produce actions similar to those of sympathetic nerve stimulation)

SYMPATHOLYTICS
(drugs which block adrenergic receptors & neurons and produce actions similar to those of sympathetic nerve inhibition)

SYMPATHOMIMETICS

A. According to nature:

Natural (in the body):
As adrenaline, noradrenaline & dopamine

Synthetic:
As ephedrine, amphetamine, isoprenaline, …

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B. According to chemical structure:

Catecholamines:
- Have catechol nucleus
- As adrenaline, noradrenaline, isoprenaline, dopamine, dobutamine, hexoprenaline, α-methyl noradrenaline, …

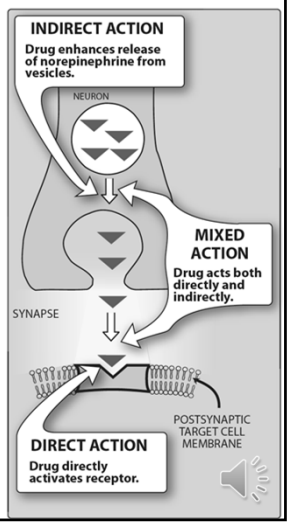
Non-catecholamines:
- Do not have catechol nucleus
- As ephedrine, amphetamine, …

C. According to mechanism of action:

Direct stimulation of adrenoceptors:
As adrenaline, noradrenaline, isoprenaline,…

Indirect by:
- Release of NA as amphetamine
- Inhibiting uptake-1 of NA as reboxetine
- Inhibiting MAO as phenelzine
- Inhibiting COMT as entacapone

Dual or mixed mechanism (direct + indirect):
As ephedrine



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D. According to receptor selectivity:

α-receptor agonists:
- Selective α_1 agonists: as phenylephrine & methoxamine
- Selective α_2 agonists: as clonidine & α-methyl NA
- Non-selective $\alpha_1 + \alpha_2$ agonists: as oxymetazoline

β-receptor agonists:
- Selective β_1 agonists: as dobutamine
- Selective β_2 agonists: as salbutamol
- Selective β_3 agonists: as octopamine
- Non-selective $\beta_1+\beta_2+\beta_3$ agonists: as isoprenaline

α+β receptor agonists:
- $\alpha_1+\alpha_2+\beta_1+\beta_2+\beta_3$ agonists: as adrenaline
- $\alpha_1+\alpha_2+\beta_1+\beta_3$ agonists: as NA
- $\alpha_1+\beta_1$+D agonists: as dopamine

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Please, if possible, try to stick to the following scheme to discuss a drug or a group of drugs:

NAME of the Drug or Group

- Def.: a few words about source and important properties.
- Classification (position): if a group (classification), if a drug (position).
- Pharmacokinetics: absorption, distribution, metabolism & excretion.
- Pharmacodynamics: mechanism of action, action (therapeutic & adverse).
- Pharmacotherapeutics: indications, contra-indications, precautions.
- Drug toxicity: if any, manifestations & approach.
- Drug Preparations: brand names.

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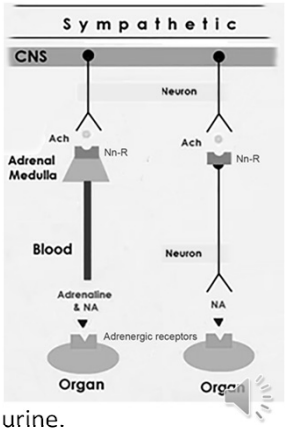
ADRENALINE

- Def.:

Adrenaline or epinephrine is a natural catecholamine present in adrenal medulla and some neurons in CNS.
Endogenously, it acts as a chemical transmitter at postganglionic sympathetic nerves except those of sweat glands (ACh).
It is unstable, oxidized in air or light → adrenochrome, red in color, toxic.
Stable in blood due to presence of glutathione and ascorbate; reducing agents.

- Class. (Position): one of sympathomimetics.



- Pharmacokinetics:

- Not effective orally
- Given locally in epistaxis
- Given by SC to lessen rate of absorption of other drugs
- Given by inhalation in bronchial asthma
- Given by intracardiac route for cardiac resuscitation

- As all catecholamines, adrenaline does NOT pass BBB.

- Neuronal uptake;
- Metabolized by MAO and COMT enzymes → excreted in urine.

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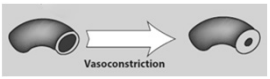
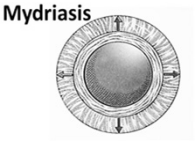
ADRENALINE

❑Pharmacodynamics:

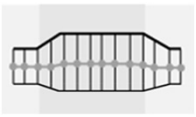
-M.O.A.: Adrenaline acts by direct stimulation of all subtypes of adrenoceptors ($\alpha_{1,2}$ & $\beta_{1,2,3}$).



- Local actions:
  - Skin & m.m.: vasoconstriction (α) of SC and submucosal bl.vs.
  - Eye: decongestion; decrease synthesis of aqueous humor (α) → ↓ IOP
  - Bronchi: dilation (β_2) & decongestion of bronchial mucosa (α).



-Systemic actions:
  - CNS: anxiety (no/very mild stimulation)
  - Eye: active mydriasis (α_1)
  - Heart: (β_1) +ve inotropic; +ve chronotropic; +ve dromotropic → ↑COP.
  - Bl.Vs: skin, mm, renal (α_1 mainly) → VC → ↑ TPR.
    sk.m, mesenteric (β_2 mainly) → VD → ↓TPR
    coronary (β_2) → dilation
  - Bl.pr: hypertension (systolic)



  - RS: Bronchodilation (β_2); decongestion of bronchial mucosa (α_1)

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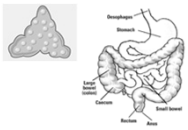
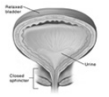
ADRENALINE

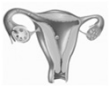
- GIT: viscid salivation (α_1)
  spasm of sphincters (α_1)
  relaxation of the wall (β_2)



- UB: spasm of sphincter and trigone (α_1)
  relaxation of the wall (*Detrusor urinae* muscle) (β_2)
  urine retention

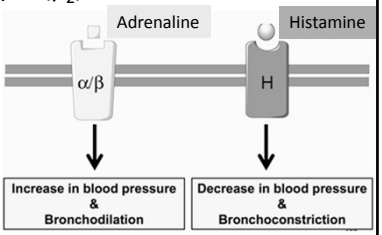


- Uterus: variable but relaxes nonpregnant uterus (β_2)



- Sk. M: VD of skeletal vessels (β_2); ↑ glycogenolysis (β_2)
  anti-fatigue effect

- Anti-allergic effect: **physiological** antagonist to histamine



- Endocrine: enhances release of cortisone.

- Metabolic: hyperglycemia [↑glycogenolysis in liver (β_2) & ↓insulin release (α_2) plus cortisone-mediated > insulin release (β_2)]; ↑ lipolysis (β_1 & β_3).

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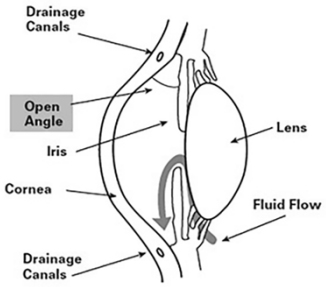
ADRENALINE

❑Pharmacotherapeutics:

❑Indications:

- With local anethetics except cocaine (as it inhibits uptake-1 & MAO)
- In epistaxis as haemostatic nasal pack
- In open angle glaucoma as eye drops (as prodrug Di-pivalyl epinephrine; Dipivefrine)
- Cardiac arrest
- Acute bronchial asthma
- Acute allergies and anaphylaxis
- Acute hypoglycemia



❑Contra-indications:

- Around fingers & toes and in circumcision
- Hypertension
- Cardiac arrhythmia, thyrotoxicosis, digitalis & volatile general anesthesia.
- MAO inhibitors

❑Precautions:

Should be used under medical supervision.

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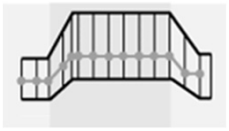
NORADRENALINE

❑Def.:

NA is a natural catecholamine present in all postganglionic sympathetic neurons (except sweat glands, in which transmitter is ACh), adrenal medulla (20%) and some neurons in CNS.

❑Pharmacology:



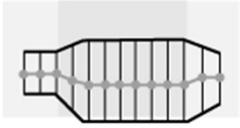
- **M.O.A.:** NA acts by direct NON-selective stimulation of $\alpha_{1,2}$ mainly & little $\beta_{1,3}$ but NOT β_2.
- **Actions & Uses :** as Adrenaline without β2 effects and applications.

ISOPRENALINE

❑Def.:

Synthetic catecholamine; not present in the body.

❑Pharmacology:



-**M.O.A.:** Isoprenaline acts by direct NON-selective stimulation of $\beta_{1,2,3}$ but NOT α receptor.

- **Actions & Uses:** as Adrenaline without α applications.

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EPHEDRINE

Ephedrine is a NON-catecholamine alkaloid obtained either naturally from *Ephedra vulgaris* plant and/or prepared synthetically.
It is a sympathomimetic as adrenaline **but with some differences**:

	Epinephrine	Ephedrine
Nature	Natural catecholamine	Natural & synthetic NONcatecholamine
Kinetics:		
Absorption	Not effective orally	Effective orally
Distribution	CanNOT pass BBB	Pass BBB
Metabolism	Rapidly by MAO & COMT	Not metabolized
Duration	Short	Long
Dynamics:		
MOA	Direct	Dual
Local action:		
Eye	Decongestion withOUT mydriasis	Decongestion + mydriasis
Nose	Decongestion	Decongestion → rebound congestion
Sympathetic actions:		
Potency	Potent	Weaker
Onset	Rapid	Slower
Duration	Short	Longer
CNS actions:	No/Mild	Potent CNS stimulant
Uses	Acute attacks	Prophylaxis
Adverse effects	Unwanted α & β	Unwanted α & β and CNS

19

SYMPATHOLYTICS

These are the drugs which block adrenergic receptors & neurons and produce actions similar to those of sympathetic nerve inhibition.
They are classified according to their **site** of action into:

- **A. Adrenergic RECEPTOR blockers:**
  - α-blockers (sub-classified, see next)
  - β-blockers (sub-classified, see next)
  - α & β-blockers as labetalol & carvedilol (used in Pheochromocytoma)
- **B. Adrenergic NEURON blockers:**
  - Catecholamine synthesis inhibitors as metyrosine
  - Catecholamine storage inhibitors as reserpine
  - Catecholamine release inhibitors
    - Guanethidine
    - α_2-agonists as clonidine
- **C. Adrenergic ganglia blockers:** as hexamethonium..!!!

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Alpha adrenoceptor blockers

Def.: These are the drugs which antagonize the α-effects of adrenergic drugs.

Classification:

Sub-classified according to site of action into:

A- Nonselective α-blockers
- phentolamine & tolazoline
- phenoxybenzamine

B- Selective α_1-blockers
- prazosin, doxazosin & terazosin

C- Selective α_2-blockers
- yohimbine

D- Other drugs with α-blocking effect
- ergot alkaloids

General uses:
- hypertension
- peripheral vascular disease

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Ergot alkaloids

Def.: alkaloids obtained from *Ergot* which is a fungus grows on Rye.
Members: ergotamine, ergotoxine and ergometrine
Pharmacodynamics:
- M.O.A.: direct blocking of α-receptors
- Actions:
  - although α-blockers that should produce vasodilation, yet they have more powerful direct SPASMOGENIC action with net result of vasoconstriction, (particularly, ergotamine & ergotoxin).
  - oxytocic effect (particularly ergometrine).
  - HYDROGENATION of ergot leads to ↑ α-blocking effect & ↓ spasmogenic effect on bl.vs., e.g., dihydroergotoxine (hydergine) → VASODILATION.
  - METHYLATION of ergot leads to ↑ spasmogenic oxytocic action on the uterus, e.g. methylergometrine.

Therapeutic uses:
- ergotamine & ergotoxin: Migraine, better taken plus caffeine (Cafergot)®
- ergometrine: Uterine inertia, retained placenta, postpartum hemorrhage, to help involution of the uterus & uterine prolapse.

Contra-indications:
- peripheral vascular disease
- pregnancy
- hypertension
- liver & kidney disease

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Beta adrenoceptor blockers

Def.: These are the drugs which antagonize the β-effects of adrenergic drugs.

Classification:

According to receptor selectivity into:

A- Nonselective β-blockers

Propranolol, Pindolol, Timolol
- Oxprenolol, Nadolol

B- Selective β_1-blockers (Cardio-selective)

- Atenolol, Acebutolol
- Metoprolol, Bisoprolol

C- Selective β_2-blockers

- Butoxamine

D- β-blockers with vasodilating activity

- Labetalol, Carvedilol, Nebivolol…

According to lipid solubility into:

A- Lipophilic β-blockers

- Propranolol, Oxprenolol, Metoprolol → pass BBB with CNS side actions

B- Lipophobic β-blockers

- Atenolol, Nadolol → don't pass BBB with minimal CNS effect

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Indications:

- Angina pectoris (caused by cardiac overload).
- Cardiac tachyarrhythmia
- Thyrotoxicosis
- Hypertension
- Varices & aneurysm
- Open angel glaucoma (Timolol)
- Anxiety and panic disorders
- Prophylaxis against migraine

Contra-indications:

- Prinzmetal's angina (caused by coronary spasm or stenosis).
- Heart failure
- Hypotension
- Diabetes mellitus
- Bronchial asthma
- Peripheral vascular disease
- Alone (withOUT α-blockers) in pheochromocytoma
- Sudden stop of treatment with β-blockers → severe relapse

Precautions:

- Adjustment of doses of co-administered drugs.
- Monitoring lipid profile, glucose and K^+ levels.

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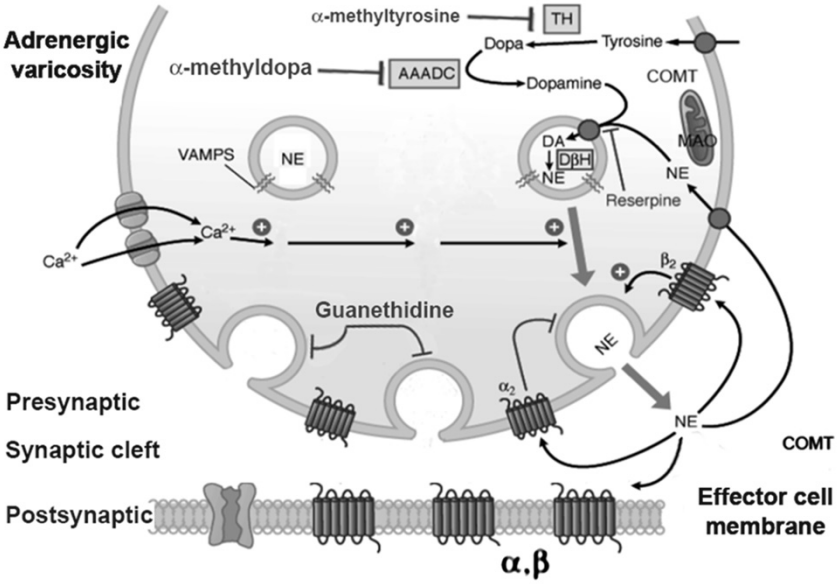
Adrenergic NEURON blockers

Def.: These are the drugs which interfere with synthesis or storage or release of adrenergic neurotransmitters.



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Adrenergic NEURON blockers

Def.: These are the drugs which interfere with synthesis or storage or release of adrenergic neurotransmitters.

Synthesis inhibitors

Members: - α-methyltyrosine (metyrosine), α-methyldopa (Aldomet)

Pharmacodynamics:

M.O.A.:

- α-methyltyrosine blocks the synthesis of NE by inhibiting tyrosine hydroxylase.
- α-methyldopa is an inhibitor of aromatic *L*-amino acid decarboxylase, and is—like dopa itself—successively decarboxylated and hydroxylated in its side chain to form the putative "false neurotransmitter", methylnorepinephrine.

- Actions:

- Sympatholytic.

Therapeutic uses:

- α-methyldopa can be used in pheochromocytoma
- α-methyldopa is useful as central antihypertensive as the formed α-methylNE is a selective α_2-receptor agonist that ↓ central sympathetic outflow, ↓ release of NE & ↓ release of renin; and it is safe on the fetus during pregnancy.

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Storage inhibitors or depletors

Member: - Reserpine (Serpasil), it is an alkaloid from *Rauwolfia serpentina* plant.

Pharmacodynamics:

M.O.A.:

- Reserpine irreversibly inhibits granular Mg^{++}-dependent ATPase that is responsible for granular uptake & storage of NA & dopamine. By the occurred inhibition the neurotransmitters are hydrolyzed by MAO & COMT leading to depletion of catecholamine stores within CNS & PNS.
- The same occurs for 5-HT stores.

- Actions:
  - Sympatholytic giving the upper hand to parasympathetic arm.
  - Major tranquilizer, due to depletion of the excitatory stores of NA & 5-HT.

Therapeutic uses:

- Hypertension
- Psychosis

Contra uses:

- Psychic depression
- Parkinsonism
- Peptic ulcer

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Release inhibitors

Member: - Guanethidine (Ismelin), Guanadrel & Bretylium

Pharmacodynamics:

M.O.A.:

- Guanethidine acts at the sympathetic neuro-effector junction by inhibiting or interfering with the release of NE, NOT at the brain (canNOt pass BBB) or adrenal medulla.
- It is taken up by NE transporters; once inside the terminal it blocks the process of exocytosis & release of NE in response to arrival of an action potential.
- Furthermore it is being gradually concentrated in vesicles, replacing NE. This leads to a gradual depletion of NE stores in the nerve endings.

- Actions:
  - Sympatholytic → AS IF → parasympathomimetic

Indications:

- Hypertension
- Glaucoma as eye drops

Contraindications:

- Pheochromocytoma
- Peptic ulcer

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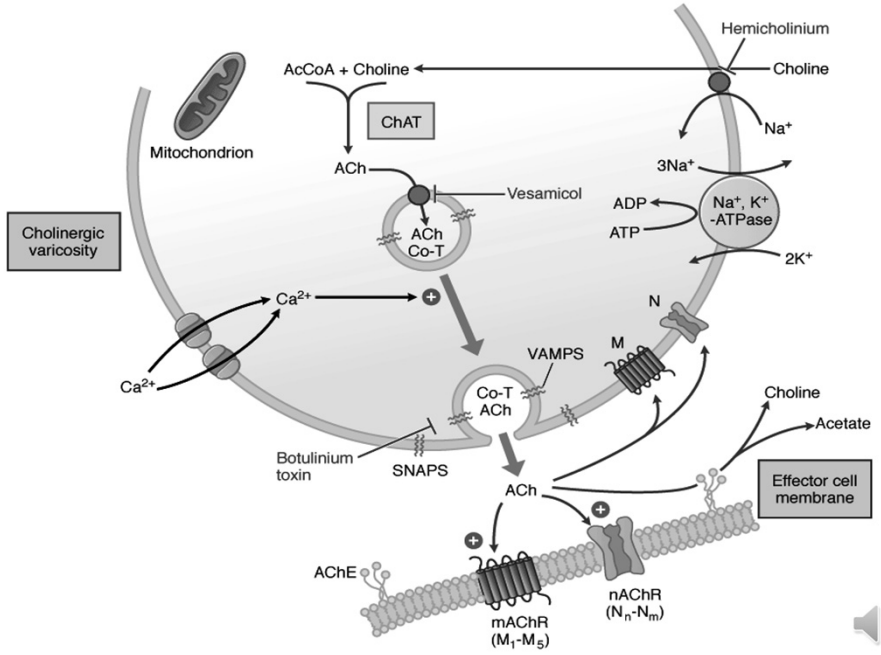
PARASYMPATHETIC DIVISION



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CHOLINERGIC RECEPTORS

Def. : Cholinoceptors are membrane bound receptors either coupled with G-proteins or with ligand-gated ion channels, specific to ACh & their antagonists.

Types:

Muscarinic (M) or Peripheral cholinergic receptors:

TYPE	LOCATION	MECHANISM	AGONIST	ANTAGONISTS
M1	Gastric parietal cells, CNS & presynaptic	$G_q \rightarrow \uparrow PLC \rightarrow \uparrow IP_3$ & DAG $\rightarrow \uparrow Ca^{++}$	ACh	Atropine Pirenzepine
M2	Cardiac M., Sphincters, & presynaptic	$G_i \rightarrow \downarrow AC \rightarrow \downarrow cAMP$	ACh	Atropine Gallamine
M3	Smooth M., Exocrine G., Endothelium & CNS	$G_q \rightarrow \uparrow PLC \rightarrow \uparrow IP_3$ & DAG $\rightarrow \uparrow Ca^{++}$	ACh	Atropine

Nicotinic (N) or Central cholinergic receptors:

TYPE	LOCATION	MECHANISM	AGONIST	ANTAGONISTS
N_N	Autonomic ganglia, adrenal medulla & CNS	Gated to Na^+ ion channel	ACh	Nicotine LD
N_M	Skeletal muscle (motor end plate)	Gated to Na^+ ion channel	ACh	d-Tubucurarine

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CLASSIFICATION OF PARASYMPATHETIC DRUGS

CHOLINERGIC STIMULANTS
(drugs which stimulate cholinergic receptors & neurons and produce actions similar to those of parasympathetic nerve stimulation)

CHOLINERGIC DEPRESSANTS
(drugs which block cholinergic receptors & neurons and produce actions similar to those of parasympathetic nerve inhibition)

CHOLINERGIC STIMULANTS

A. Direct stimulants, they directly stimulate M & N receptors:

- **Choline esters:**
  - Natural: ACh
  - Synthetic: Methacholine, Carbachol, Bethanechol
- **Choline alkaloids:**
  - Muscarine, Nicotine, Arecoline & Pilocarpine

B. Indirect stimulants, They ↓ ChE → Accumulation of endogenous Ach

- **Reversible:** Edrophonium, Physostigmine, Neostigmine, …
- **Irreversible:** Organophosphates as Echothiophate, …., ….

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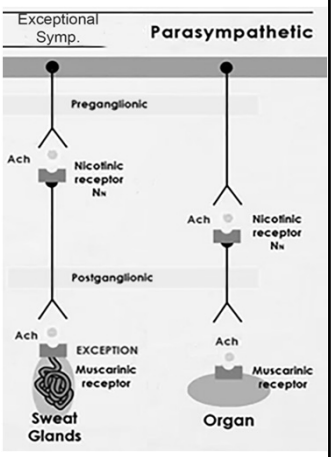
Natural CHOLINE ESTERS
ACETYLCHOLINE

Def.: Natural choline ester present endogenously. It is the chemical transmitter at:

- All postganglionic parasympathetic nerves
- Exceptional postg. **symp**. nerve to sweat glands
- All autonomic ganglia, parasymp. & sympathetic
- Neuromuscular junction
- CNS



Pharmacokinetics:

- ACh is highly ionized → of low lipid solubility
  → canNOT pass BBB & distributed extracellularly.
- Not absorbed orally
- Metabolized by ChE into choline & acetic acid.

Pharmacodynamics:

- **M.O.A.:** direct activation of both M & N receptors.
- **Actions:**

Acc. to the type of activated receptor, Ach has two types of actions:

Muscarinic actions | Nicotinic actions

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A) Muscarinic actions:

- ↑ *Constrictor pupillae* muscle (M3) → miosis
- ↑ ciliary muscle → accommodation of the eye to near vision
- ↓ IOP via wide angle filteration
- ↑ lacrimation - conjuncvtival vasodilation

- ↓S-A node → -ve chronotropic → bradycardia (M2)
- ↓A-V node → -ve dromotropic → delays conduction to ventricles
- ↑ non-innervated M3 receptors on endothelium → release of EDRFs as NO → vasodilation → ↓TPR
- hypotension due to bradycardia and low TPR

- Bronchospasm & increased bronchial secretion (M3)

- ↑ peristalsis, ↑ secretions (M3), ↓relax sphincters (M2) → defecation

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-↑ *Detrusor urinae* muscle (M3), ↓relax sphincter (M2) → urination

-↑ myometrium (M3)

-↑ glandular secretions including thermoregulatory sweat glands (M3).

B) Nicotinic actions:

- Sk. M.: ↑ N_M receptor → contraction, twitches & convulsions
- Aut. Ganglia & Adr. medulla: ↑ N_N receptor > hypertension (**if alone**)

Therapeutic uses:

ACh is not used clinically as it is:

- Ineffective orally - of short duration - nonselective

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Synthetic CHOLINE ESTERS

Members: **METHACHOLINE, CARBACHOL & BETHANECHOL.**

Def.: Synthetic quaternary amm. Compounds with the following characters:

- Lipophobic, doNOT pass BBB & distributed only extracellularly.
- Effective orally & parenterally (SC), less metabolized by ChE → longer
- With some selectivity

Dynamics, Kinetics & uses compared to ACh:

	Acetylcholine	Methacholine	Carbachol	Bethanechol
Nature	Natural	Synthetic	Synthetic	Synthetic
Metabolized by	Both ChEs, true & pseudo	True only	Not	Not
Orally	Not effective	Irregular	Complete	Complete
Duration	Short	Longer	Longer	Longer
Muscarinic actions	++++	++++	++++	++++
Nicotinic actions	++++	±	++++	Devoid
Selectivity	No	CVS	Eye, GIT, UB	GIT, UB
Therapeutic uses	Not used clinically	Tachycardia Peripheral vascular disease	Glaucoma Postoperative Paralytic ileus & urine retention	Postoperative Paralytic ileus & urine retention

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CHOLINE ALKALOIDS

Members: **MUSCARINE, ARECOLINE & PILOCARPINE.**

Def.: Natural tertiary amines, NOT esters, therefore NOT metabolized by ChEs.

Muscarine:

- Alkaloid isolated from toxic Mushrooms (*Amanita muscaria*).
- NOT present endogenously
- Selective only on M-receptors and has muscarinic actions of ACh.

Arecoline:

- Alkaloid isolated from *Areca nut*.
- Has both nicotinic & muscarinic actions especially on GIT with CNS stimulation
- Uses as vermifuge & in folk medicine as memory enhancer chewing gum.

Pilocarpine:

- Alkaloid from *Pilocarpus jaborandi.*
- Has mainly muscarinic action especially on the eye & exocrine glands
- Uses:
  - Miotic eye drops for ttt of glaucoma & to remove adhesions between iris and lens alternatively with mydriatics
  - As sialagogue in ttt of xerostomia
  - As diaphoretic in ttt of fever
  - As hair tonic in promotion of hair growth (Tonoscalpine lotion)®

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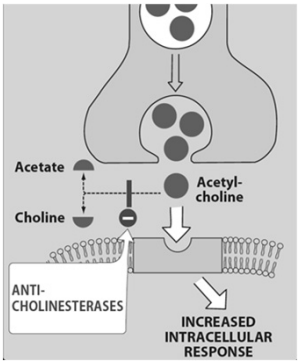
INDIRECT CHOLINERGIC STIMULANTS
ANTICHOLINESTERASES

Def.: These are the drugs which deactivate ChEs resulting in accumulation of endogenous ACh which, in turn, produces its actions, both M & N.

Deactivation of ChEs may be **reversible** or **irreversible; via** occupation of the anionic or/and esteratic active sites of ChE.

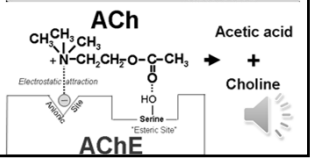


Reversible:

- **Quaternary amm. alcohols:** as Edrophonium:
  - Attach to the anionic site of ChE
  - Not a substrate for the enzyme, so not metabolized
  - Rapidly reversible, so of short duration (about 5 min.)
- **Carbamate derivatives:** as Physo- & Neostigmine
  - Attach to both sites of ChE, anionic and esteratic
  - Esters, so they are metabolized by the enzyme
  - Duration is up to 6 hs

Irreversible:

- **Organophosphates:** as Parathion, Echothiophate,
  - Attach to the esteratic site
  - Not metabolized
  - Their effect needs re-synthesis of new ChE



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EDROPHONIUM (Tensilon®)

- Synthetic quaternary amm. Alcohol, rapidly & reversibly deactivates ChE by attaching to its anionic site.
- Its action is more selective on skeletal muscle than other ChEs.
- Given by IV injection giving immediate action but of short duration (minutes).
- It was used in diagnosis of myasthenia gravis [but bradycardia is a major concern].

PHYSOSTIGMINE & NEOSTIGMINE

	Physostigmine (Eserine)	Neostigmine (Prostigmine)
Nature	Natural, tertiary amine alkaloid from *Calabar* beans	Synthetic, quaternary amm. compound
Kinetics	Absorbed orally, passes BBB, rapidly metabolized by ChE, short duration	Irregularly absorbed orally, cannot pass BBB, slowly metabolized by ChE, longer duration
Dynamics	Reversible anti-ChE More specific on the eye → miosis CNS stimulation	Reversible anti-ChE More specific on GIT & UB → ↑ wall, ↓ sph. Direct sk. muscle stimulant effect No CNS stimulation
Uses	As eye drops in: - Glaucoma - Counteract mydriatics - Alternatively with mydriatics to cut adhesions between iris & lens As IV injection in atropine poisoning	As IM, SC, PO (F < 5% of 15 mg tab) in: Myasthenia gravis (diagnosis & treatment) Postoperative paralytic ileus Postoperative urine retention Tachycardia As IV injection in curare poisoning

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ORGANOPHOSPHOROUS COMPOUNDS

Def. & Members: Synthetic compounds with many applications, including:

- Insecticides as Parathion & Malathion
- Anthelmintics as Haloxon (Antinematode) & Metrifonate (Anti-Shistosoma)
- War gases as Sarin, Tabun & Soman (OBSOLETE).
- For Glaucoma as **Isoflurophate** eye ointment & **Echothiophate** eye drops.

Pharmacokinetics:

- Have high lipid solubility > rapidly absorbed from all sites; and well distributed.

Pharmacodynamics:

- They deactivate ChE by phosphorylating its esteratic site in an irreversible manner; this leads to accumulation of endogenous ACh which stimulate both M and N receptors.
- Such irreversible effect ends by re-synthesis of new ChEs (butyryl ChE needs about 3 weeks; while acetyl ChE needs about 3 months)

Ttt of organophsphate toxicity:

- Atropine 1 mg/IV every 10 minutes till mydriasis, tachycardia & dry mouth; the patient should be kept atropinized for at least 48 hs to reverse muscarinic actions.
- Nicotinic action on sk. M. is reversed by anticonvulsants as **Nembutal** or **Diazepam**.
- ChE re-activators (Oximes) which are antidotes; as **PAM** (pyridine aldoxime methylchloride; pralidoxime), **DAM** (Di-acetyl-Monoxime); they are effective orally. PAM canNOT pass BBB while others can pass reactivating **both** peripheral & central ChEs.

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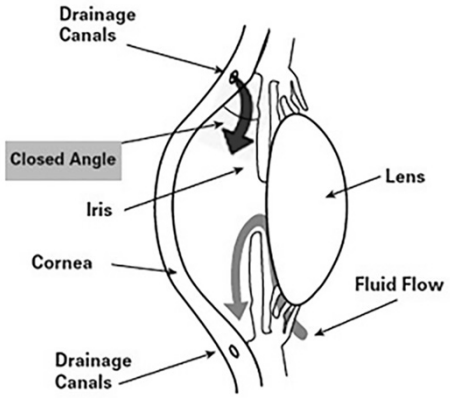
Indications of ACHEs:

- Myasthenia gravis
- Glaucoma (Closed angle)
- Counteraction of mydriatics
- Alternatively with mydriatics to cut adhesions between iris & lens
- Postoperative paralytic ileus
- Postoperative urine retention
- Tachycardia
- Alzheimer's disease



Contra-indications of ACHEs:

- Conditions and drugs associated with INCREASED cholinergic activity (N & M).

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CHOLINERGIC DEPRESSANTS

A. Cholinergic RECEPTOR blockers:

1. Muscarinic antagonists:

- **As atropine and its substitutes**

2. Nicotinic antagonists:

- Ganglionic blockers: as Hexamethonium
- Neuromuscular blockers:
  - Competitive: as d-Tubucurarine
  - Depolarizing: as Succinylcholine

B. Cholinergic NEURON blockers:

- Drugs inhibit synthesis of ACh: as Hemicholinium
- Drugs inhibit storage of ACh: as Vesamicol
- Drugs inhibit release of ACh: as Botulinium toxin

They are used mainly for their skeletal muscle relaxant effects.

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Muscarinic antagonists

Def.: These are the drugs which compete with ACh for its M-receptors.

Members: They are classified in TWO ways:

According to nature:

- Natural alkaloids: as Atropine, Hyoscine
- Synthetic atropine substitutes:
  - Mydriatics as Homatropine
  - Antisecretory as Pirenzepine
  - Antispasmodics as Propantheline
  - Antiasthmatics as Ipratropium
  - Antiparkinsonian as Benztropine
  - For urinary incontinence as Oxybutynin

According to selectivity:

- Nonselective: as atropine (Block **all** M-receptors, M1-M3)
- Selective: M1 antagonist as Pirenzepine
  M2 antagonist as Gallamine

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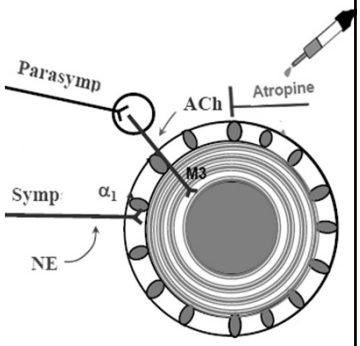
ATROPINE

Def.: It is a natural tertiary amine alkaloid obtained from *Atropa belladonna* plant.

Pharmacokinetics:

- Well absorbed orally, parenterally & from mucous membranes
- Distributed all over the body extra- & intracellularly
- Passes BBB, so it has CNS effects
- Metabolized in the liver by atropinase-hydrolysis reaction into tropic acid & tropine base; & partly excreted unchanged in urine.

Acidification of urine **increases** atropine excretion.



Pharmacodynamics:

-M.O.A.: direct blocking of M-receptors (M1-M3)

-Local actions:

- Eye:
  - Passive mydriatic (paralysis of *C. pupillae* m.)
  - Cycloplegic (paralysis of ciliary m):
    - → close canal of Schlemm →↑IOP.
    - → loss of accommodation to near vision
  - ↓lacrimation
- Skin & mucous membranes: local anodyne

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- Systemic peripheral actions:
  - CVS:
    - Tachycardia, after initial bradycardia due to central stimulation of CIC
    - ↑ A-V conduction; +ve dromotropic
    - Vasodilation (secondary to overheating due to block of sweating), flushing & fever occur in large dose (atropine fever)
    - Mild hypertensive
  - Resp. T:
    - Bronchodilation
    - Dry bronchial secretion, side effect in asthma; **Ipratropium** & **Tiotropium** are better as they has less effect on bronchial secretion.
  - GIT:
    - ↓ salivary secretion → xerostomia
    - ↓ gastric acid secretion; **Pirenzepine** & **Telenzepine** are better as they are more specific on M1 receptor.
    - Antispasmodic; **Propantheline** is better as more specific
    - Spasm of sphincters → constipation

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- UB:
  - Relax the wall
  - Spasm of sphincter & trigone
  - urine retention; **Emepronium** & **Oxybutynin** are more specific

- Skin:
  - ↓ sweat secretion (anhidrosis)

-Systemic central actions:

- Cortex:
  - Mainly CNS **stimulant** → restlessness, excitation, hallucinations, …

- M.O:
  - ↑ RC (analeptic) & CIC (explains initial bradycardia)
  - ↓ VC (anti-emetic), short duration (Hyoscine is better), unlike H_1 blockers which have long duration.

- Basal G.:
  - ↓ → anti-parkinsonian; **Benztropine** is more specific

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Indications:

- Poisoning with cholinomimetic drugs
- Ophthalmoscopic examination
- Heart block
- Bronchial asthma
- Colic either intestinal or biliary or renal
- Diarrhoea
- Peptic ulcer
- Urinary incontinence & cystitis
- Hyperhydrosis
- Vomition & motion sickness
- Parkinsonism
- Pre-anesthetic medication, to:
  - prevent respiratory depression (↑ RC)
  - prevent aspiration pneumonia (↓ salivary & bronchial secretion)
  - protect against cardiac depression (+ve chrono- & dromotropic effects)

Contra-indications:

Glaucoma
Tachycardia
Constipation & paralytic ileus
Hypersensitivity to atropine
Young (FF) and old (SPE, senile prostatic enlargement) patients

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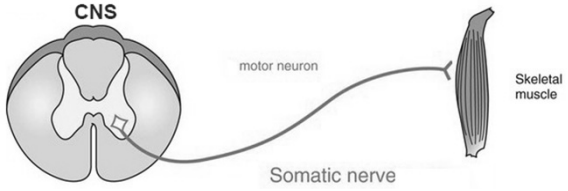
SKELETAL MUSCLES (Somatic NS)



Skeletal muscle STIMULANTS

Def. & Members: These are drugs which stimulate skeletal muscle function and **used** in ttt of myasthenia gravis.

- They include:
  - ACh and analogues acting on N_M-receptors
  - AntiCholinesterases

} (Studied previously).

Skeletal muscle RELAXANTS

Def.: These are drugs which inhibit skeletal muscle function and **used** in ttt of epilepsy and as pre-anesthetics before surgical operations.

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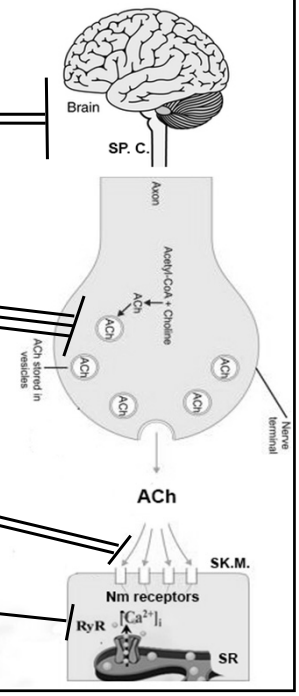
Sk. muscle relaxants are classified into:

A. Central sk. muscle relaxants:
→ **In CNS (Anti-Convulsants)**

B. Peripheral sk. muscle relaxants:

Pre
1. Drugs ↓ SYNTHESIS of ACh: as Hemicholinium
2. Drugs ↓ STORAGE of ACh: as Vesamicol
3. Drugs ↓ RELEASE of ACh: as Botulinus toxin & Mg^{++}

Post
4. Neuro-muscular blockers: subdivided into:
   - **4.1. Competitive** as Curare, Gallamine
   - **4.2. Depolarizing** as Succinylcholine
5. Direct sk. muscle relaxants: as Dantrolene; it blocks Ryanodine receptor on SR of Sk.M.



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Neuro-Muscular blockers

COMPETITIVE

- They compete with ACh for N_M-receptors at motor end plate
- They produce muscular relaxation withOUT initial stimulation
- Their effect is **antagonized** by Anti-ChEs
- Examples are:
  - d-tubocurarine, Atracurium, Cis-atra…,
- Duration: up to 30 min (longer)
- Adverse effects:
  - Histamine release
  - Bronchospasm
  - Hypotension
- Contraindications:
  - Bronchial asthma
  - Myasthenia gravis
  - With aminoglycosides & quinolones

DEPOLARIZING

- They doNOT compete with Ach for N_M receptors
- They produce initial stimulation due to depolarization, followed by depression due to persistent depolarization (partial agonists)
- Their effect is **potentiated** by anti-ChEs
- Examples are:
  - Succinylcholine (Suxamethonium)
- Duration: up to 15 min (shorter)
- Adverse effects:
  - Initial twitches
  - Muscle fatigue
  - Hyperthermia & Hyperkalemia
  - Phase-2 block
- Contraindications:
  - Peptic ulcer
  - Glaucoma
  - PseudoChE deficiency

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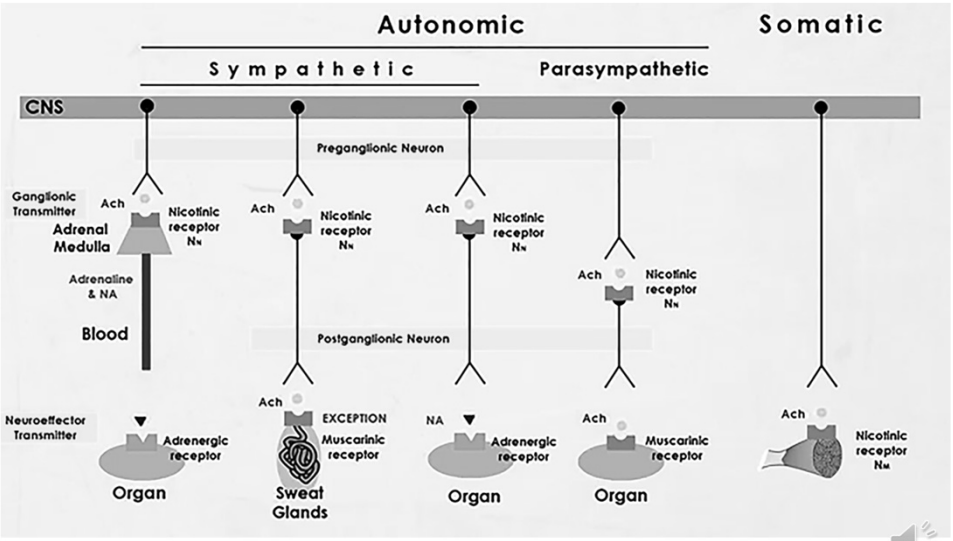
Receptors & transmitters within PNS



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