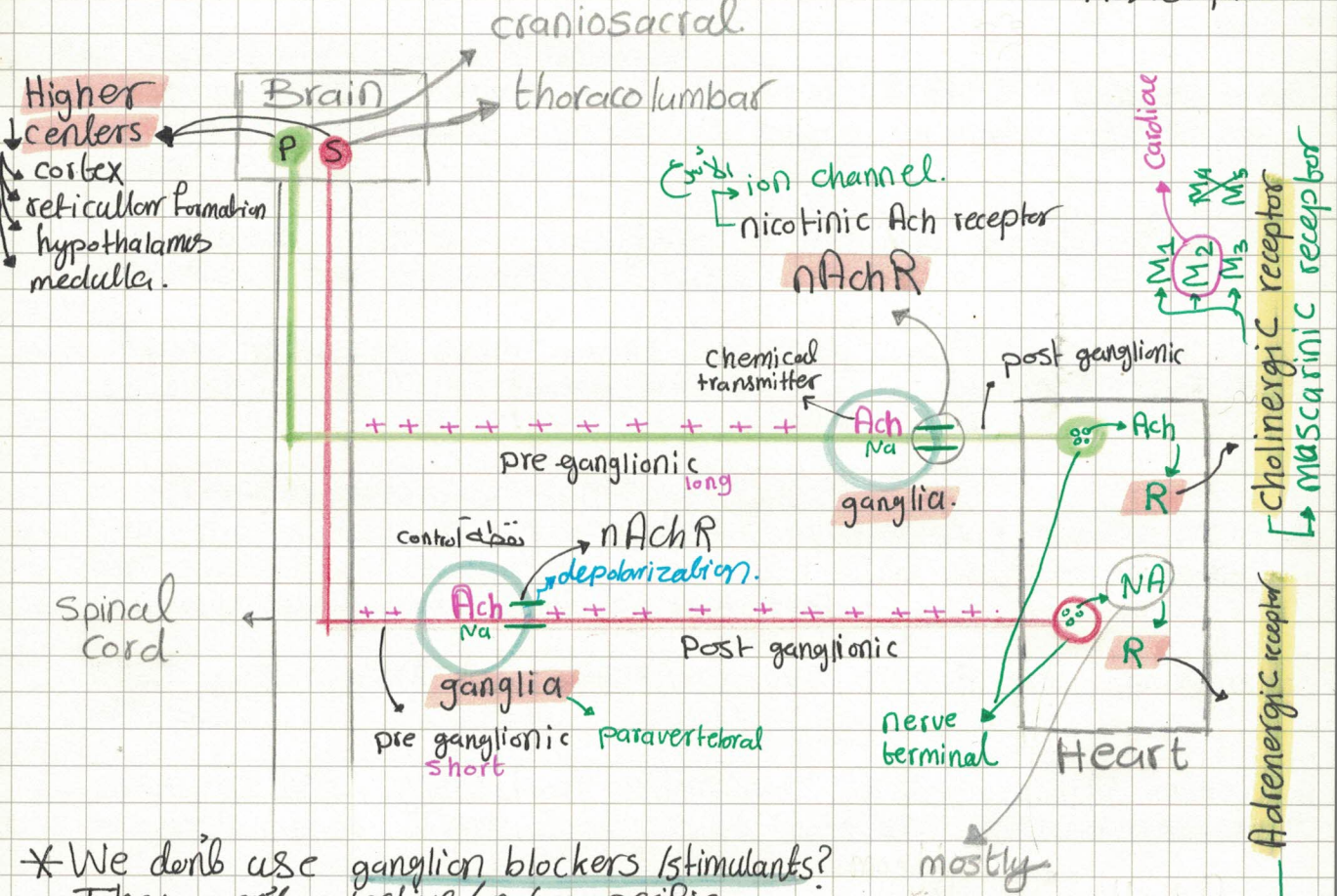
Chapter 2
Autonomic Pharmacology

1.1
1.2

P → Parasympathetic
S → sympathetic
R → receptor



* We don't use ganglion blockers /stimulants?
  - They aren't selective / not specific

usually, the major (not all) of internal organs have dual supply (s & p) nerves.

* organs with single innervation:-
  - adrenal medulla → epinephrine
  - arrector pili muscle
  - sweat gland
  - most blood vessels → sympathetic innervation.

* Patient with:-

- Tachycardia /How to treat him?
  Drug → inhibits/ blocks β_1
  → ↑ the activity / stimulate M_2

- Bradycardia
  Drug → Inhibits /Blocks M_2
  → ↑ the activity of β_2 / sympathetic system.

* Fate of ach.
  is rapid hydrolysis by cholinestrase (ChE) enzyme.
  discussed

Part 1 Basic information

The autonomic nervous system controls involuntary activity.

Sympathetic nervous system (SNS)

- short preganglionic axons originate from thoracic & lumbar areas of the spinal cord & synapse in ganglia located close to the spinal cord.
- The adrenal medulla is considered a modified ganglion & is innervated by sympathetic fibers.
- Thermoregulatory sweat glands are anatomically sympathetic, but postganglionic nerve fibers release Ach (i.e sympathetic cholinergic)

Parasympathetic nervous system (PNS)

- Long preganglionic axons originate from cranial & sacral areas of the spinal cord & synapse in ganglia located close to or within the innervated organ (with few exceptions).
- short postganglionic axons innervate many tissues and organs as the SNS.
- Parasympathetic innervation predominates over sympathetic innervation of most organs except blood vessels (have only sympathetic supply)

Enteric nervous system (ENS)

- The ENS is considered the third division of the ANS
- It is a collection of neurons inside the wall of the GIT that controls the motility, exocrine & endocrine secretions of the GIT.
- Nerve terminals contain peptides & purines as neurotransmitters
- This system functions independently of the CNS & is modulated by both SNS & PNS.

Somatic nervous system ⇒ controls voluntary activity.

- Long axons originate in the spinal cord & directly innervate skeletal muscles (no ganglia).
- Nerve terminals in the NMJ release Ach as the neurotransmitter

Neurotransmitters of ANS

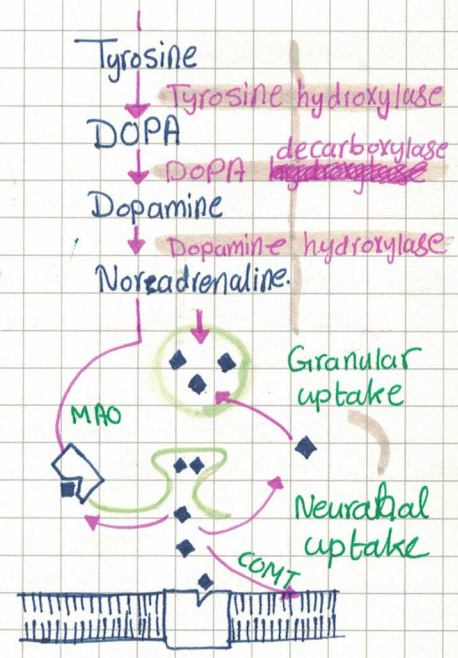
① Norepinephrine and epinephrine.

. They are catecholamines, having catechol nucleus.

Biosynthesis of catecholamines:-

. In nerve endings, tyrosine is hydroxylated by tyrosine hydroxylase to form dopa; dopa is then decarboxylated to form Dopamine which is hydroxylated into norepinephrine inside storage vesicles.

. In certain areas of the brain & in the adrenal medulla, norepinephrin is methylated by N- methyl transferase to form epinephrine.



Storage and release:-

. Norepinephrine is stored in vesicles in nerve terminals.

. Norepinephrine also exists in a non-vesicular cytoplasmic pool that is released by indirectly acting sympathomimetics (eg. tyramine, amphetamine)

Termination

Re-uptake (80%):- mainly in the form of:.

- Neuronal uptake (into neuronal cytoplasm)
- Granular uptake (into storage vesicles).

Metabolism (18-20%)

. Monoamine oxidase (MAO) enzyme:- metabolize norepinephrine in neuronal cytoplasm.

- MAO-A ⇒ present in the brain & peripheral tissue (eg. liver & intestine)
- MAO-B ⇒ present mainly in the Brain & more active on dopamine. It has little effect on norepinephrine & serotonin

. Catechol-O-methyl transferase (COMT): metabolizes norepinephrine in synaptic space.

Resorpin ⇒ medical sympathectomy

. انزلدواد ↓ prevent NE to be re-uptaked.

② Acetylcholine ACh

.Ach is synthesized in nerve terminals from acetyl co-A & choline .Synthesized Ach is stored in vesicles in nerve terminal.

.Botulinum toxin blocks Ach release and causes skeletal muscle paralysis • small amount ⇒ medically ⇒ cosmetics ⇒ botox

. The main fate of Ach is rapid hydrolysis by cholinesterase ChE enzyme, there are two isoforms.

	True ChE → acetyl ChE	Pseudo ChE → Biological scavenger
Site	. Cholinergic structures . CNS . ganglia . NMJ . RBCs.	. contract wall . contract sphincter. . plasma . liver.
Specificity	Specific for Ach. • Methacholine.	Not specific - destroys Ach. • procaine & succinylcholine & hyosine
Importance	essential deficiency is fatal	Not essential Deficiency is Not fatal.
Regeneration	In 3 months	In ~3 weeks.

③ Co-transmitters

A number of Non-adrenergic-Non-cholinergic (NANC) transmitters may be found in association with NA or Ach in the autonomic nerve terminals . They are released with the primary transmitter to play a regulatory function.

Example include :-

- neuropeptide Y
- encephaline
- histamine
- 5HT
- ATP
- PGs
- Nitric oxide NO
- purine
- serotonin
- angiotensin

Table 1. Distribution and functions of **autonomic receptors.**

Tissue	SYMPATHETIC		PARASYMPATHETIC	
	R	Effect	R	Effect
Heart	β_1	↑ all cardiac properties (tachycardia, ↑A-V conduction, ↑contractility, etc)	M_2	↓ SA node activity and AV conduction (NOT **atrial conduction)**
Blood vessels	α_1 β_2	VC of most BV VD of skeletal muscle BVs, and coronary artery.	M_3*	VD of most BV (through release of EDRF). ***N.B.*** *Most vascular M3 receptors are non-innervated*
Bronchi				
Smooth ms	β_2	Relaxation (Bronchodilatation)	M_3	Contraction (Bronchoconstriction)
Glands	α_1	↓ Bronchial secretion	M_3	↑ Bronchial secretion
GIT				
Wall	α, β_2	Relaxation (↓ motility)	M_3	Contraction (↑ motility)
Sphincters	α_1	Contraction	M_3	Relaxation
Salivary gld	α_1	↑ enzyme secretion (viscid saliva)	M_3	↑ water secretion (salivation)
Liver	β_2	Glycogenolysis		–
Stomach HCl		–	M_1	↑ HCl secretion
U bladder				
Detrusor ms	β_2	Relaxation	M_3	Contraction
Sphincter	α_1	Contraction (urine retention)	M_3	Relaxation (urine flow)
Uterus	β_2	Relaxation		–
	α_1	Contraction		
♂ **organs**	α_1	Ejaculation	M_3	Erection
Kidney	β_1	↑ Renin secretion		–
Skeletal ms	β_2	Tremors and enhancement of neuromuscular transmission		–
Eye				
Iris ms	α_1	Pupil dilatation (mydriasis)	M_3	Pupil constriction (miosis)
Ciliary ms	β_2	Relaxation (distant vision)	M_3	Contraction (near vision)
IOP	β_2	↑ aq humor secretion (↑ IOP)	M_3	↑ aq humor **drainage** (↓ IOP)
Lacrimal gld		–	M_3	↑ lacrimal secretion
Sweat gld	α_1	↑ sympathetic sweating (forehead & palms)	M_3	↑ Thermoregulatory sweating (cholinergic sweating)
Fat cells	β_3	**Lipolysis**		–
Mast cells	β_2*	↓ histamine release		–
Plasma K^+	β_2	Decrease plasma K^+ hypokalemia		–
Nerve terminals	α_2	↓ NA release		–
	β_2	↑ NA release		

* = **Non-innervated receptors** i.e. receptors are found in the organ but have **no** autonomic nerve supply. They can respond only to circulating or administered agonists.
EDFR = endothelial derived relaxing factor = nitric oxide (NO).

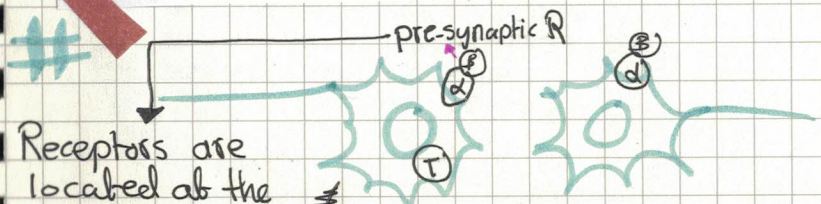
Table 2. Summary of adrenergic receptors → G-protein linked receptors

	α_1 (A, B, D)	α_2 (A, B, C)	β_1 (cardiac)	β_2	β_3 (adipose tissue)
2nd msngr	G_q (↑ IP3 & ↑ DAG) →↑ Ca^{2+}	G_i (↓ cAMP)	G_s (↑ cAMP)	G_s (↑ cAMP)	G_s (↑cAMP)
Sites and function	1. VC of **most** bl vessels (α_{1A}) 2. Contraction of all sphincters (GIT, urinary). (A, B, D) 3. Contraction of dilator pupillae ms (mydriasis) 4. Contraction of uterus 5. Relaxation of GIT & UB walls 6. Adrenergic sweating (forehead & palm)	1. **Presynaptic** nerve endings (↓ **NA release**) (more than 90%) 2. **Central:** ↓ central sympathetic outflow 3. Relaxation of GIT & UB walls	1. ↑ all cardiac properties 2. ↑ renin release (kidney) 3. adipose tissue.	1. **Presynaptic** nerve endings (↑ **NA release**) 2. **Central:** ↑ central sympathetic outflow 3. VD of sk ms bl vessels and coronary artery 4. Bronchodilatation 5. Relaxation of GIT & UB walls 6. Relaxation of uterus 7. Skeletal muscle tremors 8. ↑ aqueous humor secretion 9. ↑ liver glycogenolysis 10. ↓ plasma K^+ → hypokalemia. + Facilitation of NM transmission	↑ lipolysis (adipose tissue) → distributed more in the upper half of the body.
Sel. agonist	Phenylepherine	Clonidine	Dobutamine	Salbutamol	
Selective antagonist	Prazosin	Yohimbine	Atenolol	Butoxamine *(not used clinically)*	
Non-selec agonist	Adrenaline Ephedrine				
Non-selec antagonist	Phenoxybenzamine	Ergot alkaloids	Propranolol Timolol		

why: G_q → ↑IP_3 → ↑$[Ca^{2+}]$ → smooth msl contraction (MLCK)

K^+ dependent Ca^{2+} channel. K^+ ↔ hyperpolarization → relaxation.

- β_4 and β_5 are also present but still under investigation.
- In most smooth muscles, the α1 receptors mediate contraction through activation of Ca^{2+} dependent *myosin light chain kinase* but in the GIT smooth muscles, they mediate relaxation through hyperpolarization caused by opening of Ca^{2+} dependent K^+ channels.
- **α1** receptors have 3 subtypes, A, B, and D; **α2** receptors have three subtypes: A, B, and C.



Receptors are located at the pre synaptic membrane · to regulate transmitter release

2nd massenger
- G-protein 70%
- protein kinase
- ion channel.

nAchR → ion channel linked receptor
- the only one works without 2nd massenger

Table 3. Summary of cholinergic receptors

gastric — cardiac

	M_1	M_2	M_3	N_n	N_m
2nd msngr	G_q (↑ IP3 & ↑ DAG) →↑ Ca^{2+}	G_i (↓cAMP)	G_q (↑ IP3 & ↑ DAG) →↑ Ca^{2+}	Ion channel	Ion channel
Sites and function	1. **CNS** 2. **Stomach** →↑ HCL secretion	↓↓ SAN activity and AV conduction *(not atrial conduction)* ⇓ bradycardia.	1. **VD** of most **BV** through synthesis of *endothelial-derived relaxing factor* (EDRF) → ↓ **blood pressure.** 2. **Contraction** of all wall smooth muscles (bronchi, GIT, UB) and **relaxation** of all sphincters. 3. ↑↑ **all body secretions** (sweating, salivation, lacrimation, etc). 4. **Eye:** → miosis & ciliary muscle contraction (accommodation for near vision).	**All autonomic ganglia** and adrenal medulla	**NMJ** → skeletal muscle contraction
Selective antagonist	Pyrenzepine	Gallamine	--------	Trimetaphan	d-tubocurarine
Non-selec agonist	Acetylcholine				
Non-selec antagonist	Atropine - hyoscine				

N.B.

- **M4** and **M5** are also present in the **CNS.**
- **M1 – M3 – M5** are linked to Gq (↑ IP3 & ↑ DAG).
- **M2 – M4** are linked to Gi (↓ cAMP)

المودية
M_1, M_3, M_5
⇓
G_q
⇓
غالباً excitatory

المزجية
M_2, M_4
⇓
G_i
غالباً inhibitory

Any drug ⇒ miosis ⇒ M_3
open → trabecular meshwork → ↓ IOP ⇒ treat glaucoma

M_3 → ciliary msl. ⇒ ↑ pressure on lens → accomodation of near

Part 5 Parasympathomimetic drugs (cholinomimetics)

- The parent compound of all cholinomimetic drugs is acetylcholine
- Ach is the natural neurotransmitter in the following sites:-
  - All autonomic ganglia whether sympathetic or parasympathetic
  - Parasympathetic nerve ending to involuntary organs & exocrine glands
  - Sympathetic nerve ending to thermoregulatory sweat glands.
  - Sympathetic nerve endings to adrenal medulla.
  - Skeletal muscle motor end plate.
  - Certain tracts within the CNS. → memory
- Ach acts on both muscarinic & nicotinic receptors to produce all the effects (in the previous tables *)
  - nicotinic → skeletal muscle N_m, autonomic ganglia N_n, supra renal gland N_n
- Ach is not used clinically because: ① it has very short duration of action due to rapid hydrolysis of AChE enzyme
  ② it lacks selectivity.
- Cholinomimetic drugs are drugs that produce effects similar to Ach or cholinergic nerve stimulation, but with more selectivity & fewer side effects than Ach.

Classification of cholinomimetics drugs.

Direct-acting cholinomimetics

They act by direct stimulation of cholinergic receptors

- Muscarinic agonist
  Bethanecol, Carbachol, Pilocarpine, cevimeline
- Nicotinic agonists
  Nicotine, lobeline

Indirect-acting cholinomimetics

They act by inhibition of AchE enzyme leading to accumulation of Ach.

- Reversible ChE inhibitors.
  Physostigmine, neostigmine, pyridostigmine, donepezil
- Irreversible ChE inhibitors
  organophosphate compounds

Direct-Acting parasympathomimetics

Muscarinic agonists

Contraindication of muscarinic agonists:- Hypotension → VD

- Peptic ulcer
- Bronchial asthma
- Heart block.
- Angina pectoris (↓BP, ↓ coronary flow)
- Hyperthyroidism (AF can occur)

Pharmalogical effects :—

CVS → . ↓ AV conduction & HR (bradycardia) → stimulation of M_2
. VD → release of NO (EDRF) → ↑ cGMP → stimulation of M_3
endothelium-derived relaxing factor.

Respiratory effect → . Contraction of bronchial smooth muscle → M_3
. ↑ bronchial secretion → M_3 + bronchospasm ⇒ asthma

Eye → . contraction of constrictor pupillae muscle ⇒ miosis → M_3
. contraction of ciliary muscle ⇒ accomodation of near vision → M_3
↓ opening of the trabecular meshwork & facilities drainge of aqueus humor outflow into the canal of Schlemm
. ↓ I.O.P

GI tract → M_2, M_3 → . ↑ motility & relaxation of sphincters → M_3
. Salivation → M_3 & ↑ HCl secretions → M_1
+ stimulation of the wall → M_3

Urinary tract → . contraction of bladder smooth muscles → M_3
. relaxation of sphincters → M_3

Exocrine gland → ↑ all exocrine secretions, salivation, lacrimation, sweeting...

NMJ → . Na influx & depolarization of skeletal muscles + muscle contraction → N_m
. ↑ [Ach] ⇒ persistent depolarization ⇒ muscle weakness & paralysis.

Carbachol

. It is choline ester but resistant to hydrolysis by AchE enzyme
. It stimulates both muscarinic & nicotinic receptors.
. It is used as local eye drops to ↓ IOP in glaucoma.
→ it contracts the ciliary muscles ⇒ opening of trabecular meshwork & facilities drainage of aq. humor.

Bethanecol → M_3

. It is choline ester but resistant to hydrolysis by AchE enzyme
⇒ long duration of action (2-3) hours as compared to Ach.
. It stimulates muscarinic receptors with no activity on nicotinic receptors
. It is used to reverse post-operative urine retention & paralytic ileus (in absence of organic obstruction)
* administered orally or SC. [parenteral administration may cause cardiac arrest].

Cevimeline & pilocarpine

3ry amine. From leaves of pilocarpus Jaborandi

- cevimeline is synthetic drug - pilocarpine is a natural plant alkaloid.
- Both drugs act as muscarinic agonists with no nicotinic effect.
- Both drugs can be given orally to ↑ salivary secretions & ↓ symptoms of dry mouth (xerostomia) associated with Sjögren syndrome.
- pilocarpine is used as local eye drops to ↓ IOP in glaucoma.

Adverse effects of muscarinic agonists.

- Most important side effect include nausea, vomiting, sweating, salivation, bronchoconstriction, hypotension & diarrhea + Flushing + headache + abdominal cramps all of which can be blocked by atropine

Nicotinic agonists

① Nicotine

- It is a component of cigarette smoke. It is a poison with many adverse effects & no therapeutic benefit
- The overall effects of nicotine are complex and result from mixed stimulation & inhibition of all autonomic ganglia:-

- small doses ⇒ stimulate autonomic ganglia leading to hypertension, tachycardia, ↑ GIT peristalsis, ↑ HCl secretion & CNS stimulation.

- Toxic doses ⇒ lead to hypotension & CNS depression due to ganglion* blockade.

*Nicotine is addictive substance. Trans-dermal patches containing nicotine ~~can~~ are used to help smokers stop smoking.

② Varenicline

- It is nicotinic receptor partial agonist used for smoking cessation
- Headache & nausea are the most common adverse effects.
- Contraindicated in pregnancy & breast feeding.

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Indirect-Acting parasympathomimetics (cholinesterase inhibitors)

Mechanism & pharmacological effects

- Inhibit AChE enzyme ⇒ accumulation of Ach & stimulation of both muscarinic & nicotinic receptors.

- They are classified according to nature & duration of AChE inhibition, into reversible & irreversible inhibitors.

Reversible AchE inhibitors

They interact with AchE enzyme by making reversible bond allowing duration of inhibition lasting from minutes to hours

Physostigmine

- Natural plant alkaloid (3ry amine) that is well-absorbed from the GIT and can pass to CNS
- It can reversibly inhibit AchE enzyme for 3-4 hours, leading to:-
  - Muscarinic effects → hypotension, bradycardia, salivation, lacrimation, ↑ GIT peristalsis, miosis ---
  - Nicotinic effects → skeletal muscle contraction
  - Central effects → headache, insomnia, excitation & convulsions.

- Therapeutic uses:-
  - Because of lack of selectivity & harmful CNS effect its usually used as local eye drops to produce miosis, treat chronic glaucoma, & to cut recent adhesion between iris & lens.
  - Alzheimer dementia but newer drugs are better
  - Atropine toxicity.; it antagonize central & peripheral action.

Neostigmine

- synthetic drug (quaternary amine), that is poorly absorbed from the GIT & cannot pass to CNS.
- similar to physostigmine in mechanism & effects but no CNS actions.

- Therapeutic uses:-
  - Reverse postoperative urine retention & paralytic ileus
  - Reverse postoperative muscle paralysis resulting from the use of non-depolarizing neuromascular blocker
  - Treatment of myasthenia gravis:- it can directly stimulate nicotinic receptor at the motor end plate
  - Antidote to atropine toxicity .Glucoma.

Pyridostigmine

- Similar to neostigmine, more preffered than it in the chronic treatment of myasthenia gravis because:-
  - It has more selective action on NMJ
  - It has longer duration of action than neostigmine.

Edrophonium

- It acts as the neostigmine & pyridostigmine but has very short duration action (5-15 minutes)
- It is used in diagnosis of mesthenia gravis & to differentiate between muscle weakness due to insufficient treatment of myasthenia, or due to excessive treatment with AchE inhibitors (Tensilon test)

myasthenia gravis

=Dis an autoimmune disease in which antibodies complex with nicotinic receptors at the NMJ to cause skeletal muscle weakness.

- AchE inhibitors, such as pyridostigmine, are used to ↑ Ach levels at the NMJ to fully activate the remaining receptors.
- This ~~disease~~ disease can be diagnosed using the Tensilon test, which can also assess the adequacy of treatment with AchE inhibitors.

Donepezil & rivastigmine

- They are AchE inhibitors that act more selectively on central AchE enzyme
- Are used to ↑ Ach level in the CNS → improve memory & cognitive deficit associated with Alzheimer's disease (age-related disease.)

other drugs :- [Tarcine / Memantine] galantamine]

Irreversible ChE inhibitors

organophosphate compounds

- They include :- Drugs :- echothiophate & Isoflurophate ⇒ eye drop for glaucoma
  Thiophosphate insecticides :- Parathion & Malathion
  Ware /nerve gases :- Sarine & Soman.
- Organophosphates are highly lipid soluble & rapidly absorbed by all routes including the skin. Their ~~skin~~ CNS penetration is rapid & high.
- They interact with AchE enzyme by making irreversible (covalent bond) (phosphorylation of the enzyme)
- As time passes, the strength of the bond ↑, (a process called "aging") & AchE becomes irreversibly inhibited
- Once AchE is inhibited, Ach accumulates through the nervous system, causing muscarinic & nicotinic symptoms.
- Echothiophate is the only non absorbable organophosphate.

Manifestation of organophosphate

CVS ⇒ hypotension, bradycardia, sweating

Respiratory ⇒ bronchospasm, ↑bronchial secretions, respiratory muscle paralysis

GIT ⇒ abdominal colic, diarrhea & salivation.

Eye ⇒ severe miosis, lacrimation.

CNS ⇒ hallucinations, convulsions, & coma.

skeletal muscle ⇒ twitches & fasciculation

The cause of death ⇒ Respiratory failure.

D iarrhea & colic
U rination
M iosis
B radycardia & bronchospasm
E mesis
Excitation of CNS
L acrimation
S alivation
sweating
skeletal msl. twitches.

Treatment

- Ensure patient airway & artificial respiration
- Gastric lavage & skin wash to remove the toxin.
- IV normal saline to raise blood pressure.
- The triad :-

Atropine 1mg IV 10 minutes till ful atropinization
[dryness of mouth, mydriasis, & tachycardia]
. The patient is kept full atropinization for 24 hrs.

Cholinestrase reactivators [oximes]

Pralidoxime PAM 30mg/kg bolus dose then 8mg/kg/hr IV until clinical improvement.
. can break the bond between organophosphates & the enzyme, so the enzyme become free & hydrolyze Ach at the ~~site of~~ receptors.

Diacetylmonoxime DAM like pralidoxime, but can cross BBB & reactivate (dephosphorylate) central cholinestrase.

Diazepam 10 mg IV/IM
. to control convulsions & artificial ventilation for respiratory failure.