20/10/24

CHOLINERGIC SYSTEM

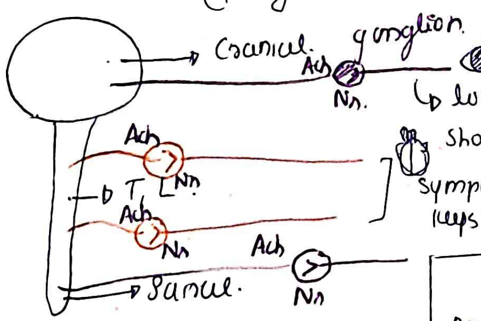
- GRG

Autonomic Nervous system

- they control activities that are involuntary - heart beat, GI motility.

ANS → (it's actually efferent parts from brain & spinal cord)
- Symp
- parasympathetic.

- whether it's sym & para depends based on where it arises from the brain/spinal cord. ↳ (purely anatomical)



- cranio-sacral outflow - parasympathetic.
- Thoraco-lumbar - outflow.

- acetyl choline is the neurotransmitter of all ~~post~~ preganglionic fibres of para & symp & post ganglionic ~~receptor~~ of is always Nn.

In para → post ganglionic NT is also Ach

∴ parasympathetic - Cholinergic system.

In sympathetic → post ganglionic NT is Noradrenaline. {no adrenaline}

∴ sympathetic → Adrenergic system

Except → Sweat glands → it's Ach
↓
but it's not para cause division is purely anatomical.

Since it is thoracolumbar outflow.
↓
we say nerve supplying sweat gland is **Sympathetic cholinergic**.

SSC

Actions. Heart

para
- rate → (-) chronotropic.
- Conduction (-) dromotropic.

no effect on contractility as ventricles doesn't even have parasympathetic innervation. 0

Symp.
+++ - Heart
- Rate → (+) Chronotropic
- Conduction → (+) dromotropic
- contractility → (+) Ionotropic

	Activate (contracts)	Inhibit (~~relax~~)	Others
Broncho	bronchoconstriction	Bronchodilation	
GIT	diarrhea	constipation	
Bladder	Urine outflow	↓	
Glands	Secretion	↓	
pupil	Miosis - contraction	mydriasis	

Summary of actions

in heart → sy → +++ (3)
para → -- (2)

rest of systems (opposition) : symp → ↓ contraction.
para → ↑ contraction.

except - compliment.

Sexual → para - erection. (Point)
symp - ejaculation (Shoot)

Cholinergic System

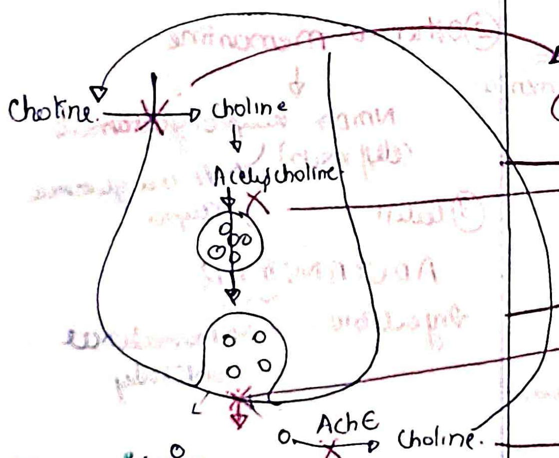
→ parasympathetic System

• Craniosacral.

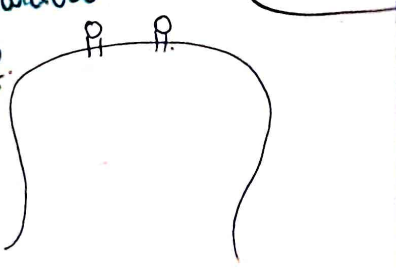
C - III, VII, IX, 10 (3, 7, 9, 10) nerves
cranial
rest - somatic
Spinal nerves 2, 3, 4 origin.

• neurotransmitter → acetylcholine.

Synthesis of acetylcholine



Black widow spider toxin?



Cholinergic Receptors.

- Nicotinic (N)
  - NN
  - NM
- Muscarinic (M).
  - M1, M2, M3
  - M4, M5

N-N → nerve - nerve junction. → ganglia

N-M → N-muscle → NMJ.
→ they need optimal stimulation

no over, no under } muscle weakness in over & under.

M1 → (CNS) → stomach. → ↑ HCl

M2 → heart → ↓ HR.
↓ conduction
(no contractile).

M3 → GIT - diarrhoea.
B Bladder - ↑ urination
B pupil → miosis
B glands → ↑ secretion.
G Bronchus → constriction.

Choline uptake inhibition. → Hemicholinium.
(-) parasympathetic activity.
behave like sympathetic.

inhibits vesicle formation → VESAMICOL.
(-) para

prevent exocytosis → Botulinum toxin.
(-) para

Inhibit ach degradation
↓
physostigmine.
(+) parasympathetic.

pehle ghas piyo, phir dal lagayo, badli sub badmasi

Parasympathetic

- (+) → parasympathomimetic or cholinergic drugs
- (-) → parasympatholytic or anticholinergic drugs.

Parasympathomimetic/ cholinergic drug.

- Directly → bind to receptors → Ach like function.
- Indirectly. → block AchE enzyme → thereby ↑ Ach.

Directly acting

1. Pilocarpine → pupil M3
   → miosis
   glaucoma - Angle closure glaucoma
2. Bethanechol M3
   Bladder - contract
   → ↑ urine output
   → Atonic bladder after anesthesia
3. Methacholine M2
   myocardium
   used in tachycardia.
4. Carbachol
   Common → M & N

Indirectly acting.

- reversible inhibitors → Clinical uses.
- Irreversible inhibitors → not clinically used → poison

Indirectly acting drugs
↓
Inhibit AchE - Enzyme.

- Reversible
  - Water soluble → neostigmine
  - Lipid soluble → physostigmine
- Irreversible

Tertiary	Quaternary amine.
NH_3	NH_4^+
↓ Physostigmine. (unionised) Lipid soluble.	↓ Neo. (ionised). (lipid insoluble)
↓ Can cross membrane. GIT, Eye, Blood Brain barrier	↓ route of admin → injections
↓ Can give orally	

eye - miosis.
↓
eye drops.
↳ physostigmine can be used in ACG as drops and can be given orally

Neostigmine → Not used in glaucoma treatment

Q) directly acting cholinergic drug used in glaucoma treatment —

Q) Indirectly acting cholinergic drug used in glaucoma
① - pilocarpine ② - physostigmine.

Atropine.

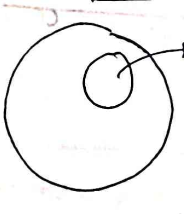
atropine is a muscarinic receptor blocker.
It blocks all M receptors.

- In CNS → we have muscarinic receptors.
- Atropine poisoning → blocks M receptors.
  ↓
  can cross BBB.
  ↓
  problem !

Treatment
Inhibit AchE → so ↑ Ach
↓
Indirectly acting.
↓
lipid soluble (so cross BBB).
↓
physostigmine ✓
Neostigmine ✗.
50% → for CNS
50% → for others.

∴ DRUG OF CHOICE (DOC) for Atropine poisoning
↓
PHYSOSTIGMINE

Senile dimentia / Alzheimers. dimentia.



→ Basal nuclei of Meynert.
↓
Memory.
↓
Cholinergic fibres.

⇒ >60years → Cholinergic fibres degeneration ⇒ memory loss.
↓
↑ ach - treatment
↓
achE Inhibitor
↓
lipid soluble → to cross BBB

Can we use physostigmine ?

physostigmine
- 50% → CNS ✓
- 50% → M1 - GIT - diarrhea; M2 → heart - brady; M3 → urination, Bowel etc. → unwanted effects.

so not used due to peripheral side effects.

TACARINE.
- → (-) AchE
- → Lipid soluble → BBB
- → 99% in CNS.

side effects.
- hepatotoxicity
- short acting - 4 times/day

Why the drug OC.

Now,
① Donepezil. Rivastigmine. Gallantamine. — • no hepatotoxicity • long acting 2x/day.

② Other → memantine
↓
NMDA receptor glutamate (clay mers). ↳ It is a glutamate receptor

③ latest
ADUCANUMAB
Injectible. ↳ monoclonal antibody

water soluble reversible ~~AChE inhibitor~~.

1. Neostigmine
2. pyridostigmine
3. Edrophonium

Oral ×, glaucoma ×, Atropine poisoning × (can't cross BBB), Alzheimer's × (can't cross mucosa, lipid membrane)

• So wherever we need to act on peripheral only and not on brain → we use them.

eg→ myasthenia gravis

Uses

- Nicotinic use
  1. myasthenia gravis — Nm. under stimulation → muscle weakness → eye-ptosis - LPS
  2. cholinergic crisis — when Nm↑↑ overstimulated called → cholinergic crisis
- Muscarinic uses.

The thing is both overstimulation and understimulation of Nm receptor leads to muscle weakness
↓
so MG & cholinergic crisis. patient will present with same problem - ie, muscle weakness.
↓
• In ER, to differentiate we use → EDROPHONIUM

Why?

• Cause edrophonium is AchE inhibitor but is short acting - only 10 minutes so

So, if symptoms improve after edrophonium.

It implies its MG (as it is due to ↓↓Nm)

If worsen, it's cholinergic crisis (as it's due to overstimulation).

EDROPHONIUM is the drug of choice for diagnosing MG & differentiating 2. → called Tensilon Test (IV edrophonium)

So for Rx of MG we use long acting drugs like-

- Neostigmine
- pyridostigmine

→ they are also Nm agonists (directly bind)

Neostigmine.
↓
Ach Esterase inhibitor.
↓
Acholine level ↑ will act on
- Nm. → Improve MG. → desired
- M_1 - HCl ↑, M_2 - HR↓, M_3 - diarrhea urination → undesired side effects → to overcome that we give an M receptor blocker - Atropine.

treatment ☆

↳ Neostigmine + Atropine.

Note: atropine has no role in treatment of. MG. It is just used to reduce the side effects of Neostigmine.

So, won't Ach bind to N_N receptors ?

yes, it does but we need higher dose of. Neostigmine for that.

M — 1x

N_m - 2x

N_N - 500x. (very high).

So, in qnty where Nm is stimulated, M will already be stimulated, that's why we use Atropine - who only block M receptors. (not N)

Nicotinic use.

① myasthenia gravis.
② Cobra bite.

Cobra venom is neurotoxic.
ie, it affect NMJ.
↓
blocks NM receptors
↓
produce muscle weakness.

treatment → Neostigmine + Atropine.

but specific / treatment of choice – is Antivenom

• (N+A) → only for symptomatic use.

③ Reversal of action of muscle relaxants.

muscle relaxants either.
- overstimulate → short acting
- understimulate → blocker → eg: Atracurium, pipecuronium. long acting ✓ preffered ✓.
(both act at NMJ.)

→ DMR are used during surgery.
→ after surgery, we have to reverse their action.
treatment use → Neostigmine + Atropine.

Muscarinic uses.

① post operative paralytic ileus.
② post operative urinary retention.

sometimes after surgery, some structures will not recover from paralysis,
↓
to relieve that.
↓
ie, ileus & urinary retention
↓
Neostigmine without Atropine
or
Bethanecol.

Irreversible Ach Esterases inhibitors

- Organophosphates ↓ malathion, parathion → highly lipid soluble.
- Carbamates ↓ carbaryl, propoxur.

⇒ they are not clinically used drugs
⇒ they come as poisoning cases.

• see, OP is very highly lipid soluble.
↓
they can even cross skin and get into blood.
↓
so suicide attempt is not the only cause, spraying it can also be fatal if sufficient amount reach blood.

• that why maam said, OP poisoning any admit, first clothes remove & oxygenate.

OP irreversible inhibit AchEsterase.
↓
Ach ↑
↳ M_1 – ↑ HCl
M_2 – ↓ HR, ↓ BP
+ Cornea M_3 → pin point pupil
→ diarrhea
→ invol. urination. etc.

pin point pupil conditions.
↓
① O P ×2
- • OP
- • opioid.
- • phenol (carbolic acid)
- • pontine hemorrhage.

pin point pupil only occurs in these conditions
↓
So must know

S – salivation ↑
L – lacrimation ↑
U – urination
D – diarrhea
G – GIT ↑
E – emesis, miosis

★ The 100% specific sign of OP poisoning is pin point pupil + ↑ secretion
Combination
↓
This occurs only & only in OP poisoning

prev Question → pin point pupil
but ↓ secretion → everyone wrote
op poisoning X
It was actually opioid poisoning.

AIIMS.

pin point pupil + ↑ secretion
but (HR↑ BP↑)

options →
OP ✓
opioid
phenol.
pontine hem.

so, how did HR & BP ↑
↓
it is theoretically possible cause.
OP poisoning → ↑ Ach.
↓
can bind to NN
too.
↓
of NN of sympathetic
↓
HR↑, BP↑.
only theoretically, cause
we said Nn = 500x dose.
so high poisoning cases only
AIIMS asks --rare will be
asked.

Treatment

• Atropin → drug of choice.

Route - IV.
② repeated every 5 minutes.
↓
Q why repeat per 5 min?
① can't we give high dose
initially?.
Q) till when to give Atropine.
①

① we only want to competitively
inhibit OP.
↓
since we don't know how much
OP is taken initially,
we just give Atropine repeatedly
in small doses rather than giving
all at same time.
↓
if we give too much
↓
Atropine poisoning.
↓
harder to treat than OP
poisoning.

② we give atropine till we
see signs of Atropinization ☆

① midriasis → easily checkable
② ↓ secretions → most specific ☆
③ tachycardia

most specific / reliable is ↓ secretions
⇓
if this sign is there we can
100% say atropinisation has
occurred ☆.
↓
But not easily checkable.
(how → ↓ crepetations in lung
indicate ↓ secretions).

⇒ most easily checkable → midriasis
• but not specific ☆.
• cause midriasis is also seen in
brain death.
• midriasis is only reliable when
BP & pulse has been checked !!
Midriasis V impt sign of brain death

• Can atropin reverse
all symptoms?

• atropin is M blocker
• so it cannot reverse
Nm related muscle
weakness

☆ Atropine cannot reverse
muscle weakness.

Next used drug →.
AchE Reactivators.

• they are oximes.
→ pralidoxime. (PAM)
→ Diacetyl monoxime (DAM)
☆ they are not DOC ☆
• they reverse / reactivate
the inhibited Acetylcholine
esterase enzyme.

☆ O O O ☆
Oximes only in OP
never in carbamates ☆
(it is contraindicated).

PAM → peripheral only
DAM → Donopleu mein
bhi karuga.

(Q) diagnosis - OP poisoning - line of management? what are the specific antidotes? how are they useful?

→ anticholinesterase poisoning.

→ organophosphates are irreversible indirectly acting cholinergic drug, that binds to acetyl choline esterase enzyme - irreversibly.

• Incidence → OP are used as agricultural & domestic insecticides.
  → OP poisoning is common

• Cause → accidental, occupational, suicidal, homicidal.

• Exposure → Inhalation.
  Ingestion
  skin contact

Mechanism of action

• organophosphates are powerful inhibitors of acetyl cholinesterase. - bind to esteratic site
↓
acetylcholine —acetylcholinesterase→ acetate + choline.
  └ organophosphates
does not occur.
↓
acetyl choline accumulation.
↓
continuous stimulation of receptors.
with eventual paralysis of nerve or muscle.

Symptoms

• kerosene like smell.

(1) muscarinic symptoms.

Heart.
→ fall in BP, bradycardia / tachycardia.
  cardiac arrhythmia, vascular collapse.

gland.
→ lacrimation, salivation, sweating,
  copious tracheobronchial secretions.

B, B
→ involuntary urination & defecation, colic.

B
→ bronchospasm, breathlessness,

eye.
→ miosis - blurring of vision
  pin point pupil.

muscles.
(2) Nicotinic symptoms
→ muscular weakness, respiratory paralysis

CNS.
(3) Central.
→ Irritability, disorientation, tremors
  ataxia, convulsions, coma, death.
  ↓
  due to respiratory paralysis

Diagnosis
→ History of exposure
→ clinical features
→ cholinesterase concentration test

Treatment

(1) decontamination & termination of further exposure to poison.
  → expose to fresh air
  → remove clothes
  → wash skin with soap & water.
  → gastric lavage by activated charcoal if needed.

(2) Supportive measures.
→ maintain patent airway, positive pressure respiration if needed,
  maintain BP, hydration - IV
  convulsions - control - diazepam.

③ Specific treatments / antidote.

Specific antidote - Atropine.

① Atropine

- Anticholinergic drug → Specifically block muscarinic receptors (only).

- It will relieve
  - muscarinic ✓
  - Central symptoms ✓ (may require higher dose)
  - not nicotinic symptoms X. (not relief for peripheral muscle weakness)

Dose

2 mg IV every 10 minutes till atropinisation.

In 24h → 200 mg maximum.

Use → upto 7 - 10 days (maintenance dose)

Atropinisation →
- dilated pupil
- bronchobronchial secretion dries up
- tachycardia.

② Cholinesterase reactivators

Oximes → pralidoxime.

mechanism of action

Oximes binds to anionic site of Acetylcholinesterase

↓

react with OP to form oxime-OP complex.

↓

oxime-OP complex dissociates and releases enzyme free

↓

thus cholinesterase gets reactivated.

Dose

- pralidoxime - 1-2 g IV given within 5 minutes of poisoning & not later than 24h.

precaution

should be given within minutes after poisoning before enzyme undergoes aging.

* not useful in carbamate poisoning as carbamate binds to both anionic & esteratic site

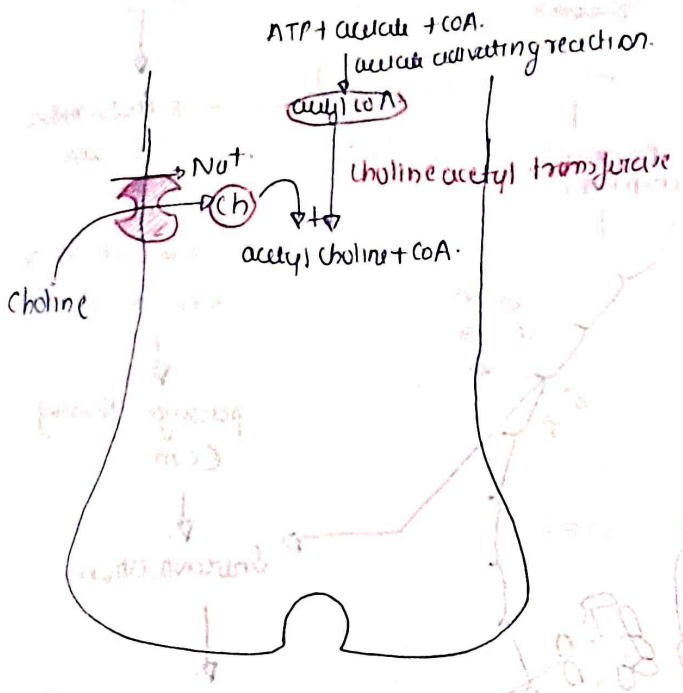
↓

It is usually contraindicated because _____.

Cholinoceptors.

- Muscarinic → GPCR
- nicotinic → ligand gated cation channel.

Synthesis, Storage & Destruction of Ach



① Choline is actively taken up by Na+-choline co-transporter present on axonal membrane.

↓

② Choline + acetyl CoA
↓ choline acetyl transferase. (acetylation of choline.)
acetylcholine + CoA.

↓

③ Acetyl choline is actively transported (is by VAT.) into synaptic vesicles and stored in them.

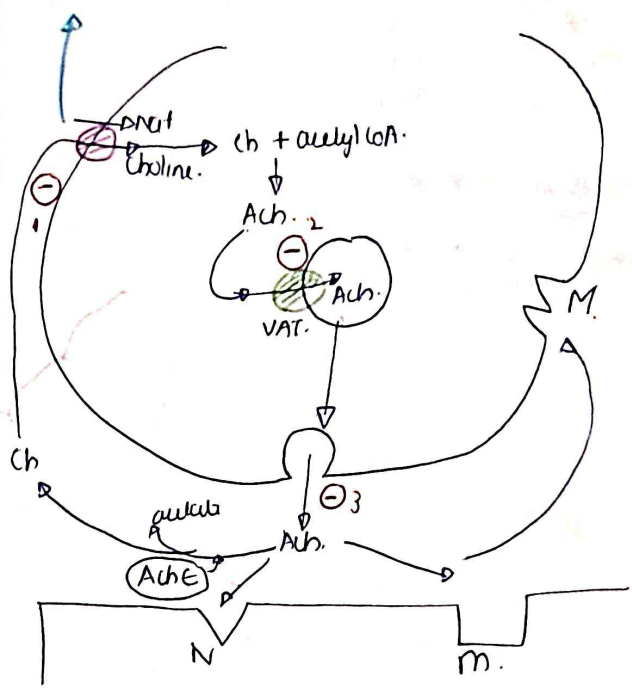
↓

④ Acetylcholine is released from nerve terminals in pulses by exocytosis.

↓

⑤ Acetylcholine.
↓ Cholinesterase.
acetate + choline → reuptake

Choline uptake → Rate limiting step



- ⊖ → Na+-choline cotransporter.
- ⊖ → Vesicle associated transporter
- $\ominus_1$ → Hemicholinium → inhibit choline uptake
- $\ominus_2$ → Vesamicol → block VAT. → prevent Ach entry to vesicle / Ach storage in vesicles.
- $\ominus_3$ → Exocytosis.
  - Inhibit release → Botulinum toxin
  - massive release & depletion. → Black widow spider toxin.

NOTE:
Botulinum toxin → causes long lasting loss of cholinergic transmission
- treatment of spastic conditions
- age related wrinkles

Cholinesterases.

- Acetylcholinesterase → @ cholinergic site → Hydrolyse Ach
- Butyryl cholinesterases. → in plasma, liver, intestine → hydrolysis of ingested esters.