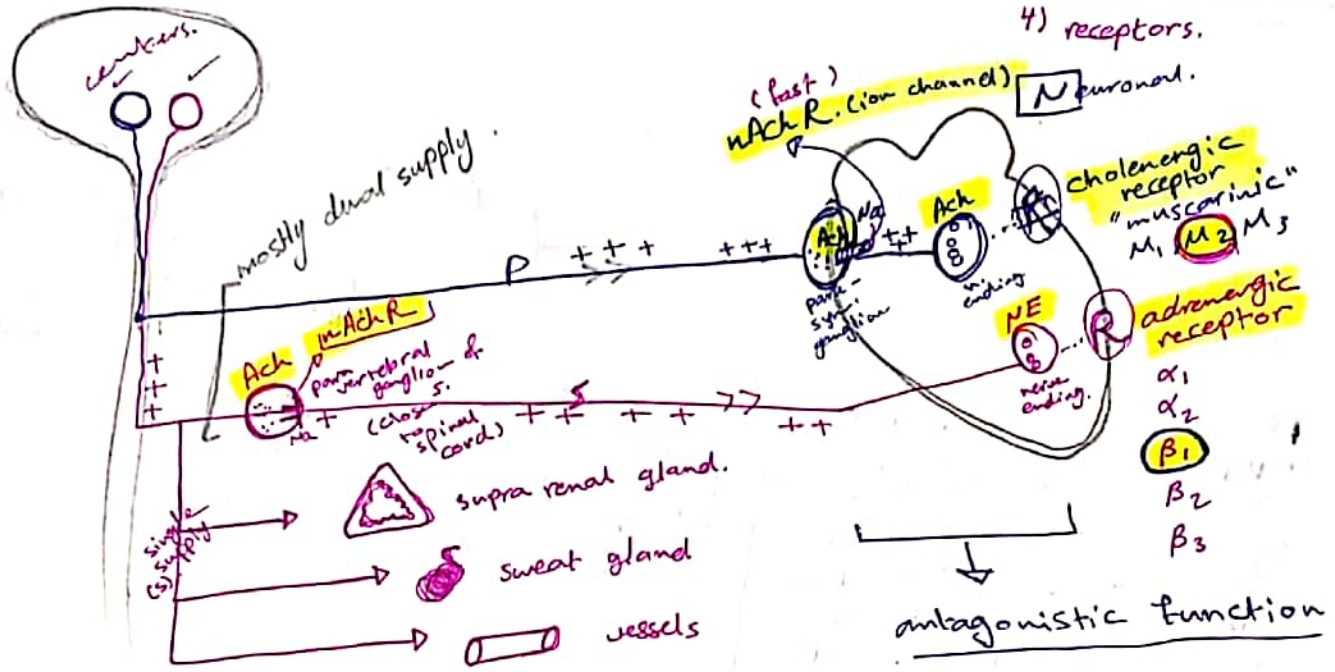
ANS / Fouda

Lec 1-2 (Review of the physiology & anatomy of ANS)

[control of the visceral functions]

1) higher centers
2) nerves
3) chemical transmitters
4) receptors.



- we can act on centers, nerve endings & receptors (by drugs) (the best choice)
  (Ach (P) vs. NE (S))
  cuz it acts specifically on a subtype of the receptors (eg. β1 blocker)

[but not the ganglia cuz it's not different between the subdivisions & we need a selective effect]

[cuz ganglionic stimulators act on the ganglia of both S. & P.

* Fates of transmitter

→ After Ach does its function it must be degraded by an enzyme (Ach esterase) which has 2 subtypes:

True Ach esterase	pseudo Ach esterase. [Biological scavenger]
specific to Ach	non specific ie. can act on - Ach. - heroin. - procaine. - succinyl choline (skeletal muscle relaxant) [in operations].
Site: ganglia, CNS, RBCs * ?!	produced in liver → plasma. (Why? ⇒ cuz it's not specific, so it can act on drugs & dietry choline esters (so that it won't accumulate in the plasma ♡).
if inhibited → you die.	not essential
3 months to be regenerated.	2 weeks to be regenerated.

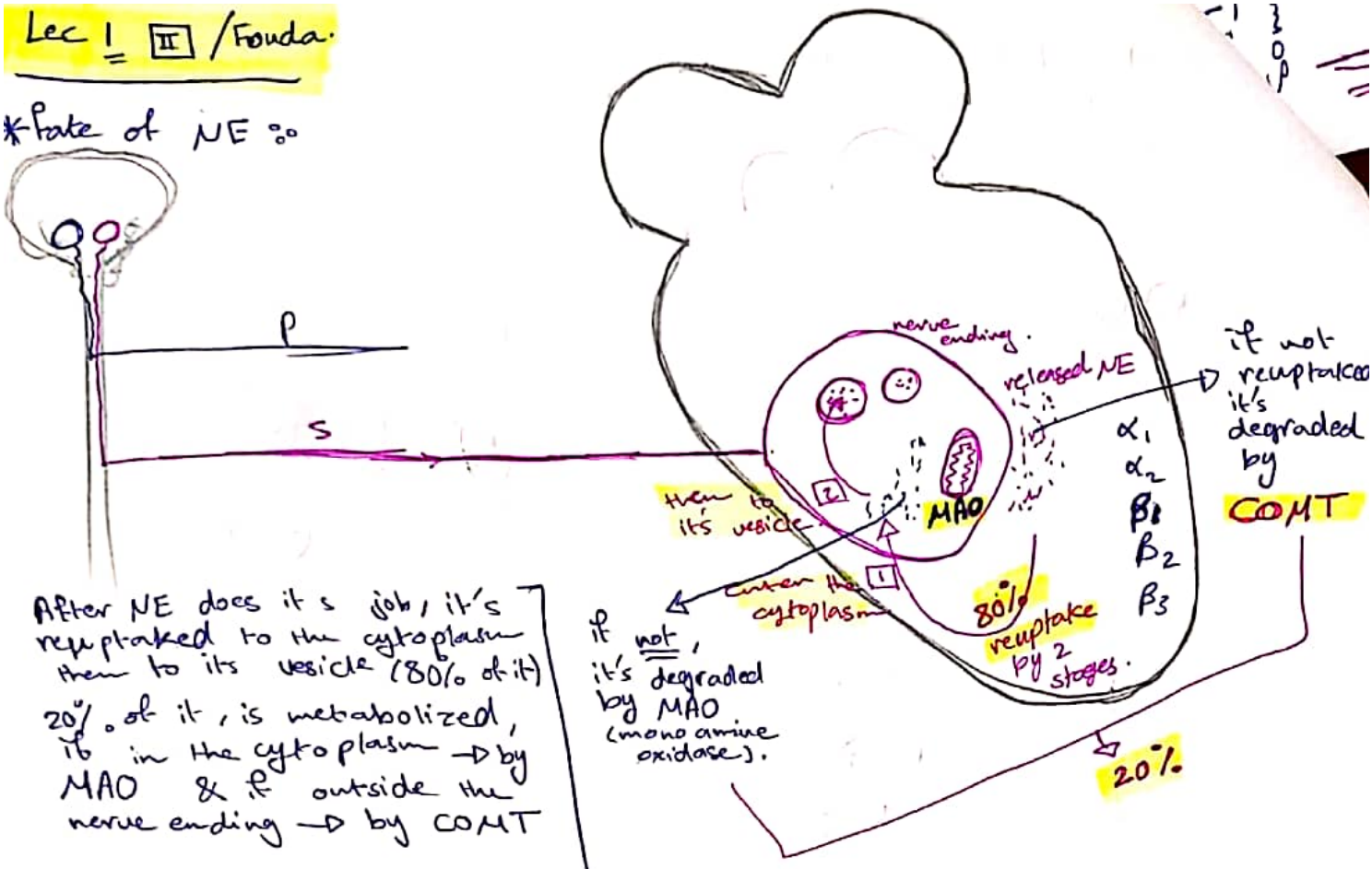
if a patient with pseudo Ach es. deficiency (or it's nonfunctional) is given succinyl choline (for operation) then the skeletal muscles will recieve 100% (instead of 10%) leading to paralysis instead of relaxation affecting respiration causing arrest

so he's given ventilator. A disease called "succinyl choline apnea"

[recall → normally 90% of succ. is metabolized in the liver so muscles recieve only 10%]

Lec I & II / Fouda.

*Fate of NE :-



After NE does it's job, it's reuptaked to the cytoplasm then to its vesicle (80% of it)
20% of it, is metabolized, if in the cytoplasm → by MAO & if outside the nerve ending → by COMT

Clinical aplication

Reserpine (used for hypertension)

it causes medical sympathectomy cuz it blocks the vesicles of NE preventing it from entering & it will be degraded by MAO, when NE is over → our sympathetic NS. is not working

MAO isozymes

A in CNS PNS

B in all but less in CNS in the Brain.

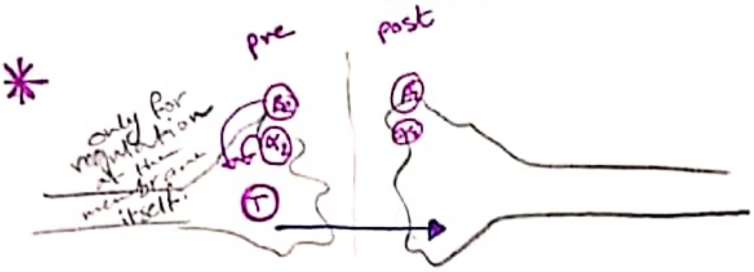
The metabolites of NE, E are → Metanephrine
if they're high → then NE, E are high. VMA (vanilline mendelic acid). normally 10%
when?!

1. stress (↑ 10 times).
2. injection (NE) (↑ 100 times).
3. rare tumor (Pen chromo cytoma) in supra renal gland. ↑ 1000 times → hypertension. 90% benign, 10% malignant.

✓ [1] presynaptic v.s. postsynaptic

[2] 2nd messenger.

Adrenergic receptors



* There's no receptor that acts directly but with the need of 2nd messenger (Gptn, kinase, ion channel...) except the ganglionic ion channel linked nAch receptor (directly, fast)

* usually 70% of receptors are Gptn linked R. & one of them Adrenergic family receptors.

NE, E — α_1, α_2, β_1, β_2, β_3

G protein linked receptors.

α_1 (subtypes A, B, D)

1. blood vessels
   - vaso constriction ($\alpha_1 A$)
2. uterus
   - contraction (not that effective)
3. eye
   - radial muscle → pupil
   - α_1 → contraction in the muscle, the pupil dilates "mydriasis"
4. GIT & urinary
   - wall relax.
   - sphincter cons. $\alpha_1 A$, $\alpha_1 D$
   - if there's urinary retention, α is responsible so we give him α_1 blocker & it worked but it caused hypotension, so we recently tried more selective ones $\alpha_1 D$ blockers.
5. sweat gland
   - only in the palm & forehead it follows the rule (not Ach) but NE & the receptor is α_1 (while the majority are by (Ach))

α_2 (subtypes A, B, C)

>90% presynaptic ⇓ no effect on the tissue but for regulation on the presynaptic membrane.

2nd messenger is (Gi) → ↓ cAMP.

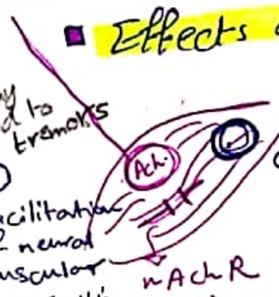
α_2 is opposite of α_1 (i.e. it's for relaxation). so, if ↑↑ NE a patient is really nervous then their α_2 don't work efficiently & we give them α_2 stimulator (agonist) → prevent ~~decrease~~ the release of NE → relaxation.

β_1 (subtypes — not yet known)

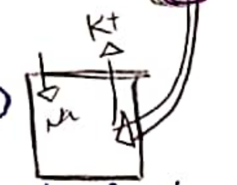
- cardiac β_1
- heart, kidney, ≈ adipocytes?
- [++], ↑heart rate, ↑contraction
- if tachycardia ⇒ we give β_1 blocker.

β_2 (during fight or flight ...)

■ Effects on skeletal muscle



1. vasodilatation (more blood is needed for better activity)
2. facilitation of neuromuscular transmission (may lead to tremors) (تفعيل الـ R (increase sensitivity) لأنه تزود الـ sensitivity)
3. shift of K+ from the blood the muscle to increase it in the muscle & (hypokalemia). for better activity.



■ on the heart: coronary artery dilatation. ∴ so V.D. by β_2 (skeletal muscle < coronary a.)

■ on the bronchi: Broncho dilatation.

■ on the liver (for sugar): glycogenolysis ∴ [↑ glucose in blood]

■ on the uterus. relaxation to protect from abortion. ♡

■ on the eye: ↑ air pressure on the eye, β_2 (press. sensors) on the ciliary epithelia → ↑ aqueous humor secretion to withstand that pressure.

→ which is a treatment for glaucoma [damage of optic nerve of the eye due to fluid building up in the front part of the eye which increases pressure inside the eye]

∴ so, in the eye :-

M_3 - in the iri's

1) meiosis (pupil constricts)
2) increased aqueous humor drainage (open trabicular meshwork + schlemm)
3) M_3 acts on the ciliary muscle which affect the lens (contraction) increasing its convexity (cuz its thickness ↑) which leads to accomodation for near vision.

→ intraocular pressure ↓

N receptors.

- skeletal muscle
  - muscular
  - N_m
  - contraction & twitches.
- ganglia of S & P
  - N_n
- one of the exceptions in the sympathetic
  - [supra renal gland (modified ganglion)
  - Ach. N_n

② use of neostigmine :

it antagonises the depolarizing skeletal muscle relaxant (to treat overdose of it) since it causes paralysis in this case).

③ neostigmine ~~↑~~

↑ [Ach] which is now able to bind & it's a direct stimulator of the (Nm) [itself]

But there's a problem : Ach → N / M → DUMBLES ⌢̈ !

it's okay ↳ Atropine (M blocker)

so it blocks the unwanted M receptors (" effects).

BTW, this's not treatment (but decreasing symptoms)

The treatment is by immunosuppressants, corticosteroids

Myasthenia gravis

a genetic auto immune disease in the muscles (the immune system synthsize antibodies against the N receptor (Nm) so Ach isn't able to bind & the patients can't contract their muscles.

طب ما فيش دوا نعطيه يقدر يشتغل زي ال Neostigmine من غير ما يشتغل ال M ؟
اه في وهو الدوا التالي.

3 pyridostigmine.

بالزبط زيه ال Neostigmine مع ملاحظة فرقين :

1. more selective to neuromuscular junction (no severe M effects)

2. Longer duration of action. (5-6 hours).

∴ that's why it's more preferred over neostigmine to treat Myasthenia gravis.

parasympathomimetics *

Indirect (irreversible) ~~drugs~~ → molecules "Organophosphates" e.g. insecticides.

- Choline esterase inhibitors
- phosphorylation of the enzyme so the molecules must contain (P)

[1] insecticides :
- malathion
- parathion.

[2] old drugs :
- echothiophate (eyedrop) [inhibits CE for 2 weeks فترة طويلة]

[3] Nerve gases (غازات الحروب، الدمار الشامل) :
- Sarine غاز الخردل (fatal)
- Soman

These molecules (contain (P)) are very very very rapidlly absorbed & bind to choline esterase covalently. [irreversible]. This bond requires 12 hours to be completely irreversible (كل ال CE يتعطل بشكل دائم)

3 hours → 50% من الانزيم هيتعطل , 12 hours → > 90% ⟹ This's called aging of the enzyme

- What would a patient who took these organophosphates look like when he comes to the emergency?

[1] CVS → bradycardia, hypotension.
[2] RS → ↓↓
[3] GIT → diarrhea.
[4] UT → urination.
[5] meiosis eye → pupil constriction (pen point pupil).
[6] sweating, vomiting, salivation, lacrimation.
[7] twitching (contraction in skeletal muscles).
[8] CNS excitation

③ GIT uses :- used for colic (due to colicy movement)
① ~~M3~~ → no colic
② ↓ secretions → so if there's diarrhea then it's recovered.

↓ بس في دوا زي (more selective)

hyoscine butyl bromide [**Buscopan**]
"**antispasmodic anti secretory drug**"

Note it's known that morphine also can reduce the motility of the GIT but it's addictive so we have a substituent of [morphine or Meperidine] called [diphenoxylate] cuz it can't cross the BBB

so, scientists had the idea of mixing diphenoxylate with atropine to make an effective drug that stops diarrhea & decrease motility of GIT called Lomotil (Nomotil).

Lomotil

diphenoxylate + **atropine**
(**morphine derivative**)

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③ M_1 ~~M_3~~ → ↓ HCl

بس الـ atropine selective
فلقنا دوا أحسن منه ↓
pirenzepine (selective to M_1)
↓ HCl **بس مش كتير**
(i.e there're a lot of much stronger drugs used instead for peptic ulcer).

Adverse effects of atropine.

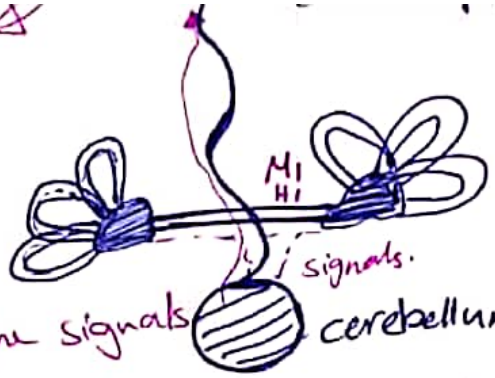
1. blurred vision
2. Dryness [more dangerous in children. ↓sweating ↑temp. *atropine fever + flushing
3. Urine retention (prostate Enlargement). *
4. glaucoma (↑IOP) *
5. Tachycardia.

غير محبذ in elderly

(6) CNS:

① motion sickness

جهاز التوازن "vestibular apparatus"



atropine prevents the signals by blocking M_1 ⇒ no vomiting in the case of motion sickness.

atropine

Hyoscine / **antihistamine**

X (M_1) X (H_1)

very effective in this pathway

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② في الدماغ الطبيعي

in the basal ganglia, that's responsible of the fine movement of your limbs, these ganglia have balanced levels of dopamine & Ach. Due to aging ⇒ Dopamine ↓ or Ach ↑ (M_1) (some people) & the person is no longer able to control the movement of limbs = "parkinson disease" مرض الرعاش

Keep the movements of your hands controlled.

حركة اليدين

Benzatropine selective to the basal ganglia

so atropine blocks M_1 to decrease Ach or we give drug increases dopamine

as long as it's in the therapeutic range.

④ urinary system.

1. cystitis (التهاب المثانة)
- urgency
- frequency
] (the need to urinate even there's no urine)

"overactive bladder" Action M3

atropine can solve this problem
[بس هو مش selective فـ في دوا أحسن منه
(oxybutinin)

2. urine incontinence (leaking urine by accident with no control).

atropine → urine retention (sphinctor يقفل الـ) : يقلل السلس
[بس هو مش selective فـ في أحسن منه
(Tolterodine)
- selective to sphinctor
- long duration

عادة عند الكبار بالسن والنساء كبار (بعد الولادة).

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⑤ eye. ① [atropine (M blocker) cause mydriasis]
(فحص قاع العين) fundus test عشان نفحص (في الحصاة)

(قطرات) tropicamide, encatropine — short duration 15 min.

or we can better use α stimulant to cause mydriasis

② To produce full mydriasis, iris edges is pulled away from the convex surface of the lens.
& this's very important in the case "Iridocyclitis" (inflammed iris & ciliary muscle)
which is [raw area able to adhese to the lens] & we give atropine derivative to prevent that adhesion] by mydriasis

☆ In this case we need the atropine itself (not substituents) cuz it's the most potent mydriatic agent + it's given as a drop (locally) so it won't induce systemic effects

[3] CNS

dose dependent ↓

1. sedative (تسكين) ← (normally Ach excitatory)
2. Amnesia (نسيان) (normally Ach memory)
3. Delirium (هذيان)
4. Hallucination (هلوسة)
   leads to (if it increase)
5. Coma → ? → Death due to RS.C.
   (lack of O_2 for few minutes in brain tissue causes cell death)
   the person becomes unresponsive & unable to reflex
   → to shut down function

SAD - HC

drug overdose ↓ Anoxic brain inju[ry] — cell death to the brain tissue → death

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★ Don't forget that atropine doesn't act on skeletal muscles cuz they have nicotinic (Nm) [not muscarinic]

- uses of atropine:
1. C.V.S → in the case of bradycardia. — cardiac (M_2 inh.)
   atropine ✓ الراعي الرسمي.
2. RS → atropine can be used in the respiratory diseases (cuz it causes bronchodilatation & less secretions) بس في أحسن منه
   [cuz it's not selective] (unwanted manifestation) centrally & peripherally SAD-HC
   بدل ما atropine ال

[Ipratropium]. ⊕N–
spray. (محلي) locally ←
can't cross BBB ←
(RS diseases)

preanesthetic medication
(قبل العملية بعمل تحضير)
is atropine مفيد
• عشان أمنع الـ secretions في ال trachea وما تلتصق ال endotracheal tube
• عشان أمنع الـ broncho constriction وال bradycardia نتيجة ال vagal stimulation.

3 GI

Normally, M_3 causes contraction of walls & relaxation of sphincter

atropine (blocker) → relaxation of walls → contraction (& relaxation)

So the patients who take atropine have constipation.

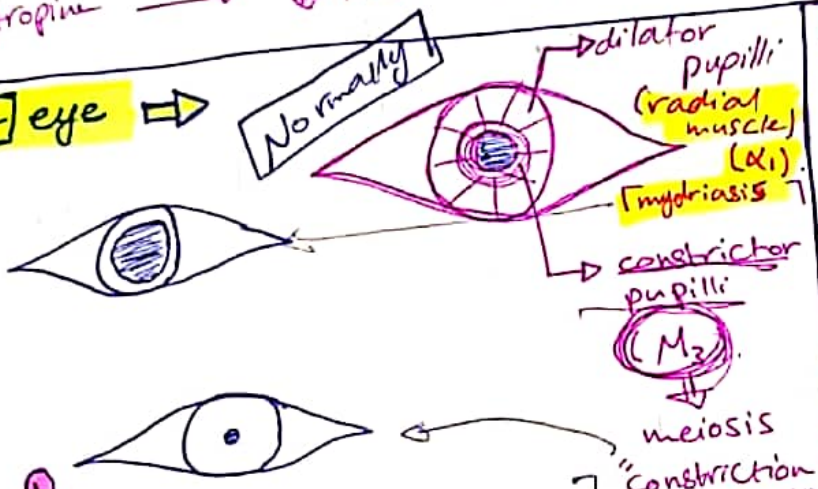
urine retention.

+

M_1, M_3 → ↑ HCl.

Atropine → ↓ HCl (M_1, M_3 blocked).

4 eye



① So when giving atropine, this (blocking M_3) allows (α_1) to cause mydriasis.

BTW, atropine is the strongest mydriatic.

② → also it causes paralysis of the ciliary muscle (convexity won't increase) so there's loss of accomodation for near vision.

5 exocrine gland.

M_3 (glandular) highly distributed in the glands (normally ⇒ ↑ secretions)

So patients who take atropine suffer from dryness. & ↑ body temp. → why
- no sweating
- no cooling

④ - ↓ lacrimation
- dryness of the eye.
- blurred vision.

mydriasis → ↑IOP

↓ lacrimation

③ → Mydriasis → (iris is retracted) → trapicular meshwork is closed → no drainage of aqueous humor → ↑ IOP

Rules

① glaucoma → atropine

② meiosis → drainage → ↓IOP.

mydriasis → drainage → ↑IOP

Lec 5 / Muscarinic blockers

① Natural [from plants]
- Atropine (prototype). [Atropa Belladonna]
- hyoscine or called [scopolamine]

disadvantages :-
1) Non selective
2) $-\overset{+}{N}-$ ( ) not ionized ⇒ can cross BBB

That's why we have better type.

② synthetic (atropine substitutents)
- ✓ more selective.
- ✓ $-\overset{\oplus}{N}-$ can't cross the BBB.

---

* Atropine :- plant alkaloid ($-\overset{+}{N}-$)

- Kinetics
  - abs. ✓
  - dis. ✓
  - metab. (liver)
  - excre. < metabolite
    unchanged

- pharmacodynamics :- [effects on the body].

① CVS

(remember that M_2 present in the atria of the heart & causes bradycardia so atropine (blocker) causes tachycardia. It has nothing to do with the contractility (cuz M_2 isn't present in ventricles).

[↓cAMP] → ↓HR

blood vessel

So Since blood vessels have M_3 but it's NonInnervated Receptor (NIR) which means.

normally M_3 has no effect on blood vessels (it's silent)

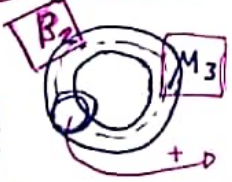
So atropine has no effects on vessels normally.

If the ligand is receptor ("ligi") is silent, then what is the effect of blocking a silent receptor?

notice that atropine overdose leads to "atropine flushing" due to toxic V.D. [not related to the direct effect.

effect on receptors]

② RS



(M_3 (acit., ↑G_q, ↑Ca^{++}, contraction)
- Broncho constriction.
- ↑secretions of the glands

Using atropine as M blocker → will block M (B.C.) & gives the chance to B_2 to cause broncho-dilatation [so atropine don't cause B.D. actively] [but passively]

• Now, how to save the life of [illegible]?

→ when you see a patient like this, you must do "rapid assessment"

Airway
clean the airways from any obstructing secretions by suction machine.

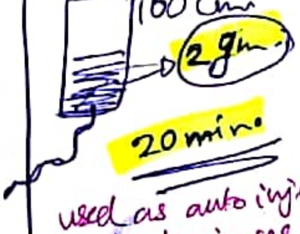
Breathing
even if you removed secretions from airways & the patient still is NOT breathing, you must use artificial respiration.

Circulation
examine 2 things.
- brady-cardia.
- BP ↓↓

→ Now drugs, **Triad**

Atropine (the most important one)
- مسؤول عن القضاء على 99% من الأعراض لأنه بيقفل M receptors
- (ampule IV) = 2mg / 5 min.
- ويبقى العيان تحت المراقبة لمدة 48 hr.
- ☆ الـ atropine ده ذاته life saving.
- → BBB ولأنه بيعدي يقفل M central & peripheral.
- → مع مراقبة
  - BP > 80
  - pulse > 80

oxime
- e.g. pralidoxime (PAM)
- diacetyl monoxime (DAM)
- "choline esterase reactivators" only by dephosphorylation (بشرط ابدريعة)
- as early as possible [before aging] = 12 hours
  - قبل ما تكون irreversible اي قبل ما تتحول
  - (غير قابلة للـ reve… ما تتفكش: carbamylation ✗ phosphorylation)
- → given parenteral



used as auto injector in schools in US for emergency.

diazepam (مهدئ، يحل عصبيك)
- 10 mg (IV).

← contin. of indirect /reversible M agonists

4 Edrophonium. أفضل من السابقين

highly selective (motor end plate بس)

its duration of action ← لكن
is only 5 minutes
يعني خيبة أملاً بس فشلها ومش لها مستخدم للعلاج (so funny).

uses

① diagnosis بل للعلاج مش مستخدم كده وعشان
ال parenteral injection عند مريض ال يعني تدي الحاجة أو تحسين تحليلات

[Tensilon test] بيسموه ← myasthenia gravis للعلاج احتياطات

prediagnosed cases with M.G ماذا تمام في ده Tensilon test ونقدر نستخدم ال

HOW?

اذا كان المريض ده تعلق للعلاج وفي الحالة هو تعبان وعنده نوبة فأنا متوقع حاجة من التنتين:

② { △1 M.G. Crisis → يعني النوبة زادت
△2 Cholinergic crisis → (in the case of overdose)
وده يعني ان Ach عالي في العضلات كتير وعمل fatigue.

In this case we use Edrophonium
if the patient (during the 5 minu.) recovers
then the problem is M.G crisis.
but if the case is worse then there's
fatigue (the 2nd prediction)
due to overdose of the treatment
(pyridostigmine).

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5 • Donepezil (new, expensive)
• Rivastigmine
] now ← previously "Tacrine"

They're like others → Cholinesterase inhibitors → but Centrally
to treat [alzheimer disease] →
- genetic disease (>65)
- loss of memory
- dementia.
- loss of cognition الادراك.

[3 theories]

① degeneration of cholinergic neurons
→ donepezil (BBB) <7% recovery.

② accumulation of infections proteins (β amyloid 42, 40) to cause insulation ...

the drug is needed to degrade these proteins &

③ The accumulation of another protein called [Tau]
degeneration of Cholinergic neurons.

2| Varnecline (like nicotine but with less adverse effects).

(agonist → N).

varnecline patch (for smoking)

Contraindicated in pregnancy.

The 2nd part of the parasympathomimetics

Indirect acting drugs

inhibit choline esterase (توقف) (so Ach isn't degraded)
وجود اللي بيشتغل مش الدوا
عشان كده indirect act

- **Reversible** (for 2-3 hours)
  رابطة ضعيفة بتتفك
  "Carbamylation"
  1. physostigmine (Eserine).
  2. Neostigmine.
  3. pyridostigmine.
  4. Edrophonium.
  5. Donepysile & Rivastigmine.

- **Irreversible**. (toxins).
  رابطة قوية بتتفاعل
  phosphorylation ودة معناه
  انه دي المركبات لازم يكون فيها phosphate وتحتها
  "organo phosphates"

physostigmine (eserine)	Neostigmine (مُهم)
it's the precursor of Neostigmine (why?!).	synthetic.
plant source	
–N– 3° amine (تتقرا)	ionized ⊕ polar –N– 4° amine
• absorbed well • ✓ BBB → since this, then it has CNS effects (↑ Ach in CNS) which is excitatory & could lead to problems	• not abosorbed well • can't cross BBB
M ✓ N ✓ CNS ✓	M ✓ N ✓ not CNS
Since it's not selective, we give it locally (موضعي), & it's the most potent meiotic. it's also an antagonist of (M blocker) atropine [in the cases of overdose] it's helpful.	① in the case of u. retention or p. ilius. (Ach → DM) دوا الحالات دي الـ indirect و الـ direct bethanechol physostig. و ينفع لكن ما فيش داعي تحط peripherally ... central ...

③ Cerimeline. — M → M3

given in the case of dryness like in:
- [sjogren syndrome]
  - (immune disease)
  - dryness in body secretions mostly eyes & mouth

it stimulates salivation

④ pilocarpine (secretions) ⇓ glands

it's given as an eyedrop like carbachol to ↓ IOP

Do these drugs have adverse muscarinic effects?
YES

D → Diarrhea.
U → urination.
M → meiosis.
B → Bradycardia. / Bronchoconstriction
L → Lacrimation.
E → Emesis (....) / excitation of CNS.
S → Salivation.

So what are the contra-indications of MR-agonists
→ bronchial asthma patients.
→ organic obstruction patients.

---

* Direct agonists of nicotinic receptors :

1 Nicotine. (tobacco) (affects the ganglia of S&P) non selective ⇒ antagonising effects. (....)

Keep in mind
- Small dose → Stimulates ganglia.
- Large dose → inhibits ganglia (depression in some functions of the body)

∴ not used in medicine

■ What is the effect of nicotine?
1. induce all ganglia → V.C.
2. stimulate suprarenal gland to produce more NE → more constriction of blood vessels
   (Ach) → adrenaline.
3. pituitary gland stimulates to secrete vasopressin (ADH) ↓ V.C.
4. endothelial dysfunction: (lining of blood vessels)

→ ↑ BP.

parasympathomimetics

receptors :

(activate cholinergic receptors).

Firstly Ach is NOT a drug, why?

1. it's not selective (act on both N, M) ↑↑ adverse effects
2. short duration (20 sec.)

[true Ach esterase v.s. pseudo " "] recall

[parasympathomimetics] (agonists)

[Direct] بيحفز ال M , N بشكل مباشر

- **M**:
  - carbachol.
  - Bethanechol
  - cevimeline.
  - pilocarpine.
- **N**:
  - nicotine
  - lobeline.

[indirect] ما بيشتغل على ال receptors بس بيعمل inhibition of Ach esterase → بيصير تكسير ال Ach قليل ف بيتجمع ال Ach و accumulation of Ach يضل شغال.

* Direct agonists of muscarinic receptors :

1. carbachol.

- * disadvantage → [M + N] ,بيشتغل في جميع الجسم كل ال receptors
- * advantage → not degraded by Ach Esterase.
  ∴ (Long duration of action).

& since it's not selective then it's not given systemically but locally in the eye as an eye drop which binds to M_3 to decrease the intraocular pressure (IOP) as a treatment of glaucoma.

2. Bethanechol .(دوا الحمامات)

(M) ← (M_3) → بس تأثيرها على GIT + UT

- relaxation in the sphinctor &
- contraction of the smooth muscles in the walls (↑ motility)

→ to push out feces & urine.

so, it's used for constipation & urine retention.

notes : [contraindications].

1. it's not given IV (only orally) or subcutaneous, cuz if IV, it could reach the heart in high dose & act on M_2 & lead to Bradycardia may leads to arrest.
2. it's not given in the case of organic obstruction (e.g. prostate enlargement) cuz even if the walls are contracted, the sphincter is NOT able to relax which leads to rupture in the walls

stones + tumor

→ so normally it's given due functional obstruction due to surgeries

Lec 3 & 4 // # Ach & similar drugs [cholinergic R]

*Recall (the distribution of Ach) so

1. nerve ending of parasympathetic division.
2. some exceptions in the S division. "sym-pathetic-cholinergic" → supra renal gland. (Ach instead of NE).
   sweat gland.
   - S → Ach → majority
   - S → NE → palms, forehead. [αR]
3. the ganglia of both S & P
4. CNS (mainly for memory).
5. skeletal muscle (recieves motor n. but the ending has Ach) (voluntary).

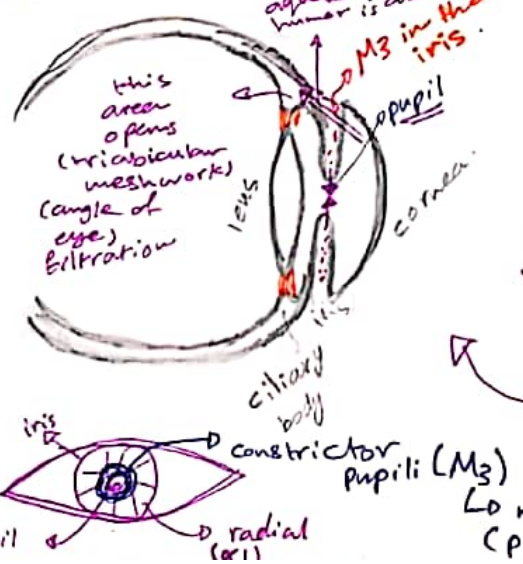
Cholinergic receptors (of Ach).

- muscarnic
- nicotinic (only in 3 places & the rest are M)
  - skeletal muscle → N_m
  - ganglia → N_n
  - suprarenal gland (modified ganglion) → N_n

	M_1	M_2	M_3
	gastric. (↑HCl).	cardiac. (↓BP).	the most abundant one
2nd messenger	→ Gq → ↑Ca++ (excitatory).	→ Gi → ↓CAMP (inhibitory).	→ Gq → ↑Ca++
	located in the gastric parital cells & responsible with M_3 of HCl.	in the supra-ventricular area & decrease SA node activity & causes [bradycardia]	(but they're only S).!
	① secretion. [M1 + M3 → HCl] / ② CNS		① in vessels. • It's Non Innervated Receptor (NIR) • it ↑ [EDRF] (NO) so vaso dilatation. endothelial derived relaxing factor. • Then what does act on it? (injected or ingested drug) (food)
			② all smooth muscles in our body. * contraction in the walls * relaxation in the sphincter to push out feces or wine. so it's activated by a drug in the cases of urine retention & constipation.
			③ any gland that has secretions [water] (sweat, lacrimal, pancreas...).
			④ eye: constrictor pupilli (M_3) ← Ach or drug. → Pupil constricts. (meiosis) → opens the angle of the eye (spongy) → absorbs aqueous humor (↓intra ocular pressure).

↑Ca++ ← Gq ← الأرباط العزيزة 1,3,5
↓CAMP ← Gi ← الأرباط الزوجية

GI, urinary bladder → M3

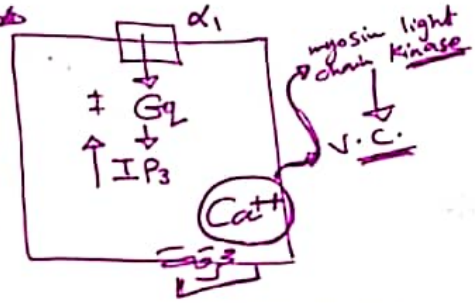


M3 internal or external M3.

meiosis (pupil constricts)

Why in all tissues α_1 cause constriction while in GI & urinary tract wall they cause relaxation?

because the Ca^{++} in the wall of GI opens Ca^{++}-dependent K^+ channel in the membranes of the cells allowing efflux of K^+ causing hyperpolarization leading to relaxation



→ no kinase in walls of GIT & UT.

β_3

mostly in the adipocytes = "lipolysis"

but it's unevenly distributed [it's located in the adipocytes of the upper half of the body] that's why it's not helpful as a treatment of obesity.

* in α_1 → 2nd messenger is G_q
* in all β's → 2nd messenger is cAMP

!!! then why β_1 causes contraction while β_2 causes relaxation since both (↑ cAMP)? cAMP have different subcellular effectors - (or different kinases). "final effectors"

$\beta \rightarrow G_s \rightarrow \uparrow$ cAMP

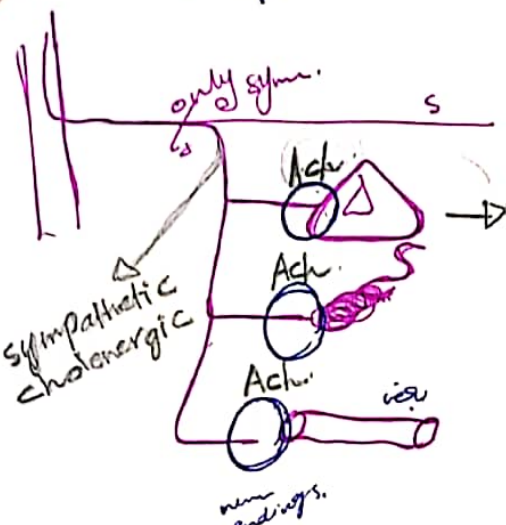
The sweat gland is one of the exceptions → [even though it recieves sympathetic innervation only] but with 2 possibilities

sympathetic → but the transmitter at the nerve ending is Ach (majority)

sympathetic GSLS → NE / E → only in palms & forehead. → Adrenergic R. α_1

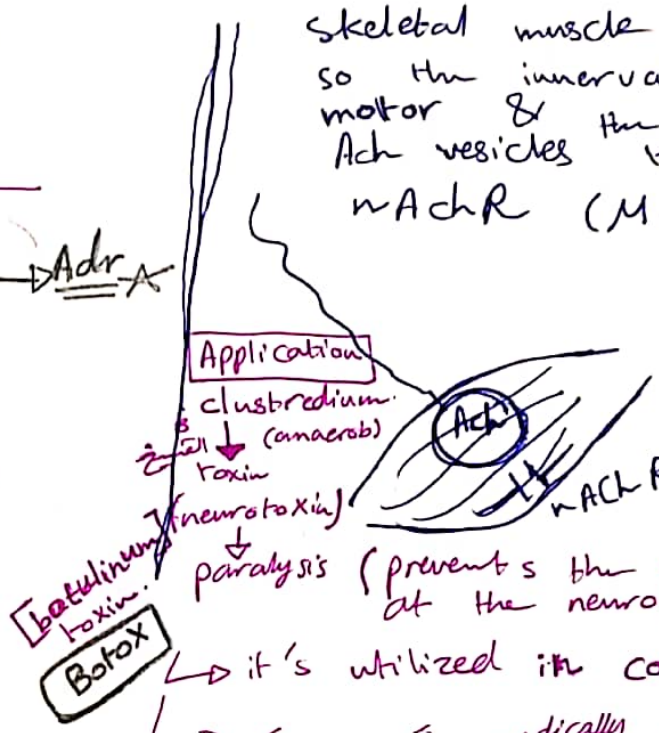
I / II

Some exceptions so



→ Adr A

Skeletal muscle is voluntary so the innervation is motor & the ending has Ach vesicles that have nAchR (Muscular).



↓ paralysis (prevents the release of the Ach at the neuro muscular junction)

↳ it's utilized in cosmetics [in very low conc.]

↳ s = s medically in spasm [= s s]

3rd division of ANS

There's local enteric nervous system (autonomic system).

(even though the intestine recieve S & P).

& if they're cut them's still peristalsis.

no NE, Ach.

NANC system [non adrenergic non cholinergic].

the majority is ↓

* Co transporters : ATP / purin, serotonin, sub. P, NO, histamine, ... with a regulatory R

(not primary like NE, Ach)./[for regulation]

also, could be found in the nerve endings of S & P in addition to NE & Ach ↓ primary transmitters.