تفريغ فارما ١

اسم الموضوع: Cholinargic Antagonists

~ lec 8 ~ Part, 1. ~

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لجان الدُّفعات

Cholinergic Antagonists

- Also called :
  - ✓ Cholinergic Blocker
  - ✓ Parasympatholytics
  - ✓ Anticholinergic drugs

الـ 3 معاني

يرتبط على الـ Receptor ويعمله Block

ويعمل Competition على الـ Receptor مع الـ Agonist فهون العم دور [efficacy, Potency]

او يكون Non Competative فلكل واحد منهم مكان ارتباط مختلف فبقلل الـ efficacy الـ Agonist

توقف عمل Parasympathetic عن طريق ايقاف عمل Ach

Pre - Ganglionic ⇒ Ach كلهم بيرتبط عليهم ⇒ Nicotonic Receptor هدول كلهم

Post - Ganglionic ⇒ هو Parasympathetic بس الـ Ach اللي بيرتبط عليه

Revision

Cholinergic Agonist

كانوا يشبهوا Ach بالـ Structure

ويرتبطوا على نفس الـ Receptors

ويعطوا نفس الـ effect

عشان افعل شغل الـ Agonist

① بعمل اشياء تشبه Ach بالـ Structure (Direct)

② بخلي مفعول Ach أطول ← كيف؟ بوقف AcetylCholineasterase (Indirect)

- Reversable ⇓ [Short Acting moderate]
- Ir Reversable ⇓ [Long Acting for weeks]

+ الدكتور حكى اسماء الـ Neurotransmitters لكل فئة منهم وموجودين ب lec ≠ بالتفصيل

+ انواع الـ Agonists (Fully, Partial, Invers)

- Bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects

- Fall into :

1. Muscarinic Antagonists
2. Nicotinic Antagonist *(clinically irrelevant)*
3. Neuromuscular - Blocking Agents *(Skeletal muscle relaxants)*

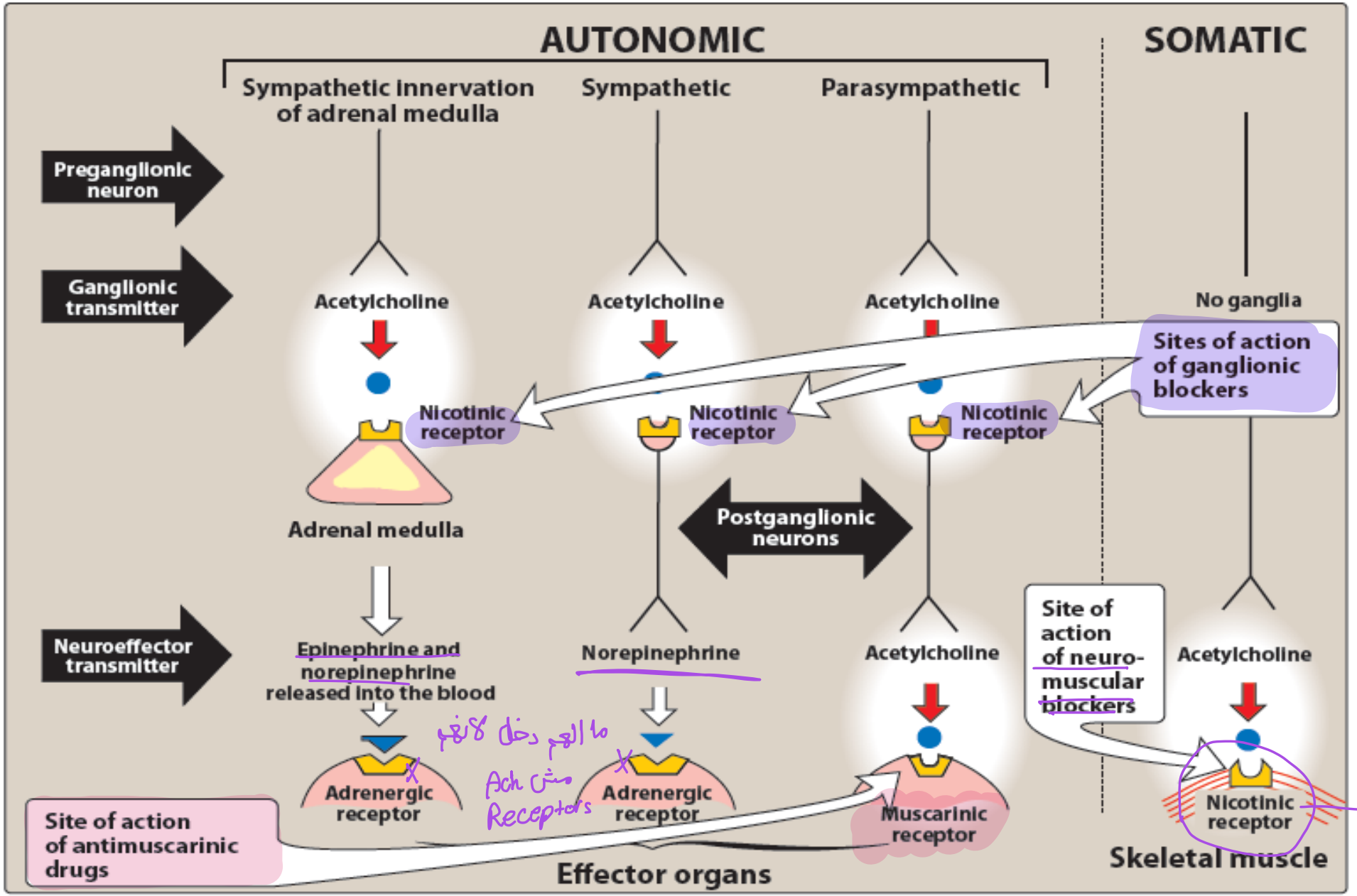


Figure 5.2
Sites of actions of cholinergic antagonists.

ANTIMUSCARINIC AGENTS

❖ Atropine

- ✓ Tertiary amine *Belladona* Alkaloid
- ✓ Competitive Antagonist to Ach on the muscarinic receptor
- ✓ Acts both centrally and peripherally
- ✓ Its general actions last about 4 hours
- ✓ Topical eye application renders it effective for days
- ✓ Mostly effective in bronchial tissues

لو حدا أخذ جرعة زيادة من الـ Atropin كيف ممكن اسيطر على حالته؟ بعطيه Ach agonist

موسع قصبات

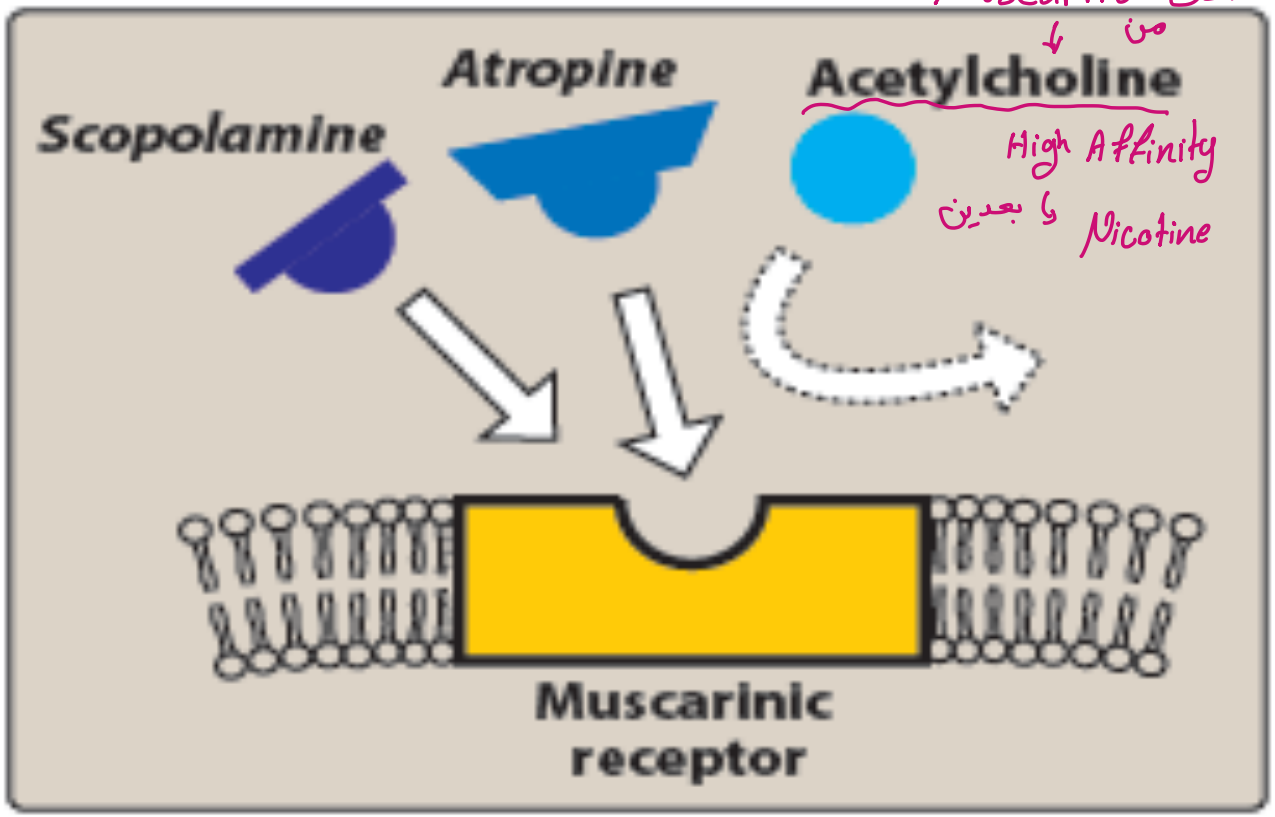


Figure 5.3
Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

Atropine Actions

- persistent mydriasis توسع في حدقة العين
- caution in glucoma ⇒ ما بصير اعطيه بكون خربت الدنيا

The most potent antispasmodic مضاد التشنج

- Decrease bladder contraction Urinary Retention
- Inhibit secretion of saliva and sweat

الفم بنشف

glaucoma

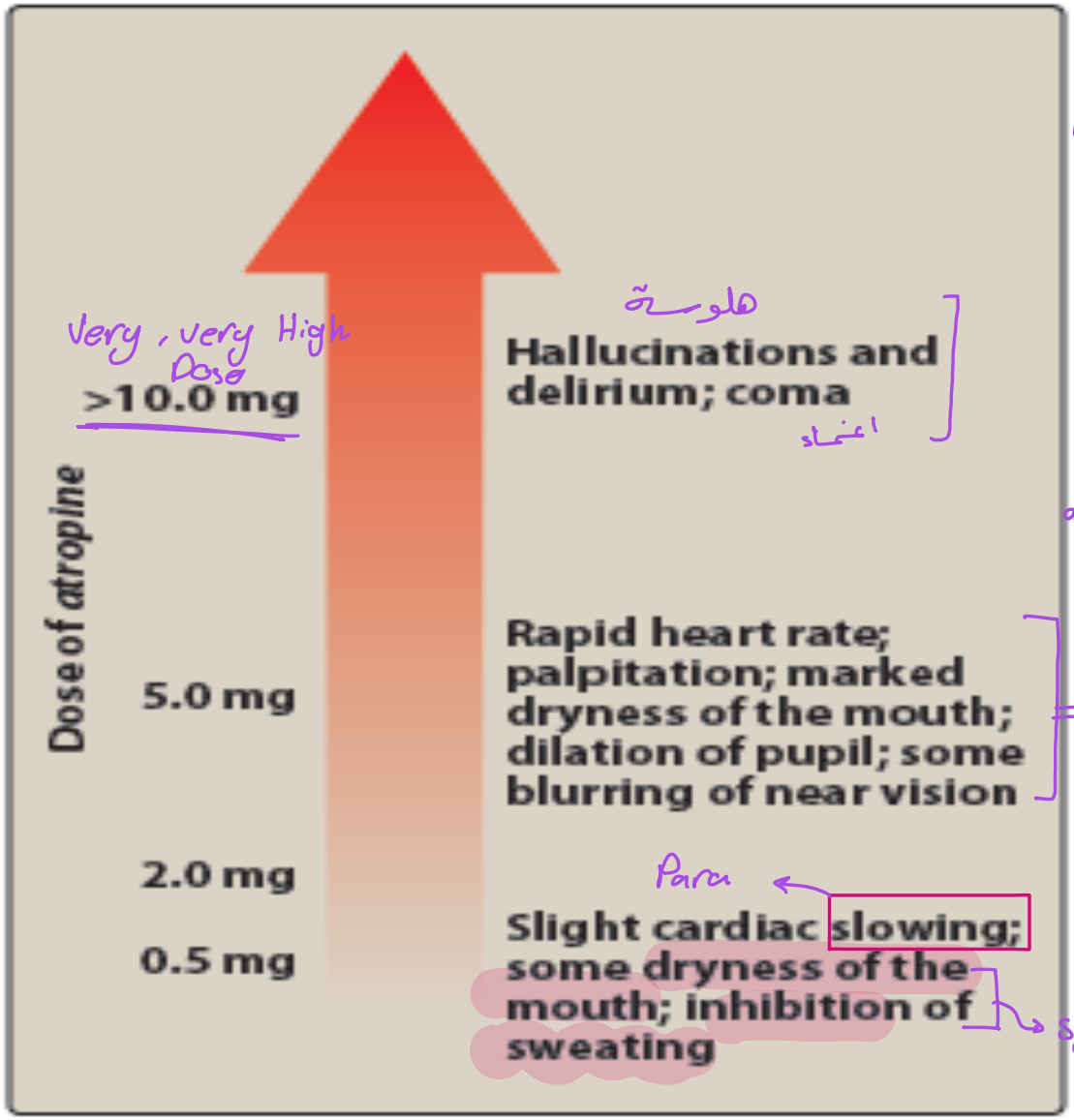
glaʊ'koʊmə, glɔ:'koʊmə / glow-KOH-muh, glaw-KOH-muh

سببها زيادة ضغط العين

noun

(eye condition)
group of eye diseases
causing optic nerve damage

Achesterase inhibitor او Cholinargic agonist عشان لعلاجها بعطي



1. Synthesis to Ach
2. Ach stored into vesicles
3. Ca^{+2} influx stimulate exocytosis of Ach vesicles
4. Ach Bind to Post-synaptic Receptor
   - Nicotonic
   - Muscarinic

OR to Pre-synaptic ← Auto receptor

at very High Dose ⇒ ParaSympathatic فبشتغل زي

⇒ sympathatic

at low Dose

- M_1 ⇒ Heart
- $M_{(2-5)}$ ⇒ Other organs ↳ sympathatic

Figure 5.4
Dose-dependent effects of *atropine*.

Atropine Actions

- Cardiovascular :
  - At low doses : Bradycardia H.R ↓
  - At higher doses: Tachycardia H.R↑
  - Arterial blood pressure is unaffected
- Atropine is the Antidot for cholinergic agonist
  - treatment of overdoses of cholinesterase inhibitor as insecticides ⇒ يكون العلاج fully Atropin
  - some types of mushroom poisoning ← فيه Muscarine ← Have high affinity to M Receptors

Adverse effects

- Dry mouth
- Blurred vision
- Urinary retention
- Constipation
- CNS related : restlessnes , hallucnations,,,
- exacerbate glucoma
- increase body temperature

Scopolamine

- ✓ another tertiary amine plant alkaloid
- ✓ *scopolamine has greater action on the CNS*
- ✓ *Scopolamine is one of the most effective anti–motion sickness* drugs available
- ✓ In contrast to *atropine, scopolamine* produces sedation.

وقائيًا

- ✓it is much more effective prophylactically than for treating motion sickness once it occurs.
- ✓ administered as patches

Motion sickness is a condition that occurs when there is a mismatch between the signals your brain receives from your eyes, inner ear, and body. It typically happens when you're in motion, such as traveling by car, plane, boat, or amusement park rides.

Symptoms of Motion Sickness

Nausea or feeling like vomiting

Dizziness or a sense of spinning

Sweating

Fatigue or weakness

Headache

Pale skin

A general feeling of discomfort or unease

Ipratropium and tiotropium

- Quaternary derivatives of *atropine*
- *Inhaled products*
- Approved as bronchodilators for maintenance treatment of
  - COPD
  - Chronic bronchitis
  - Emphysema

- *Tiotropium is administered once daily, a major advantage over ipratropium, which requires dosing up to four times daily.*

Muscarinic blockers

Trihexyphenidyl *Benztropine*	● Treatment of Parkinson disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI and lower urinary tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery
Scopolamine	● In obstetrics, with *morphine* to produce amnesia and sedation ● To prevent motion sickness
Ipratropium	● Treatment of COPD

Ganglionic blockers

Nicotine	● None

GANGLIONIC BLOCKERS

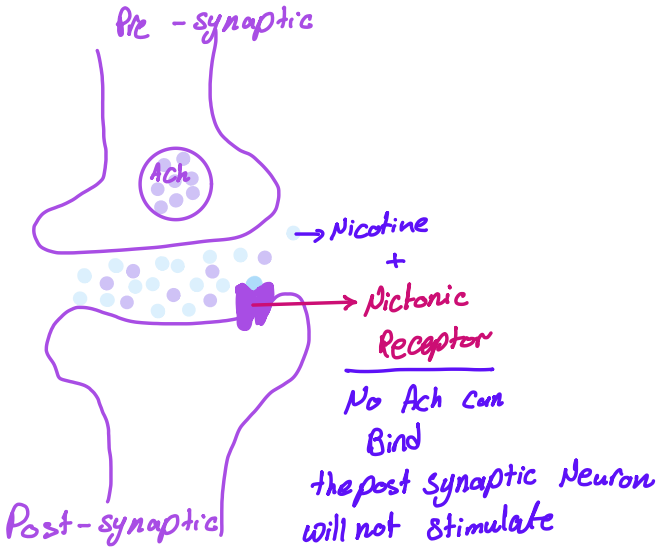
Nicotinic Receptor Blockers يرتبطوا مع كل NMJ في

- **Nicotine** : يمنع ارتباط Ach مع الـReceptor

  - A component of cigarette smoke

  - It is without therapeutic benefit and is deleterious to health. لكن ما بوقف افراز Ach

  - depolarizes autonomic ganglia, causing stimualtion (increase release of NTs) and then paralysis of all ganglia شلل



- Nicotin has complex stimulatory action
- Effects include :
  - Increase BP & HR
  - Loss of apetite
  - Sexual Arousal
  - Mood modulation

NEUROMUSCULAR-BLOCKING DRUGS

- Block choliergic transmission between motor nerve endings and cholinergic receptors in the skeletal muscles on the endplate NMJ
- They include：

❖ **Nondepolarizing (competitive) blockers**

❖ **Depolarizing agents**

Nondepolarizing (competitive) blockers

- *Curare : a toxin used to primarily to paralyse animals* ⟹ يستخدم بالتخدير
- *Pancuronium (long acting)*
- *Atracurium and vecuronium(intermediate acting)*

- binds to nicotinic recptors at NMJ and inhibit Ach binding.
- Inhibits muscle contraction
- Its action can be reverse (competively) by increasing Ach dose or using AchE inhibitors
- High doses lead to furhter irreversible blockade

- Paralysis starts with muscles of the face and eyes
- Then subsequently spreads to fingers, neck trunck
- Finally the diaphragm becomes paralyzed

- These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle.

- NM blockers are adminstered IV.
- Poor penetration of cells , BBB
- Poorly metabolized agents
- *pancuronium* is excreted unchanged in urine.

❖ S/E : hyperkalemia,IOP,

side effect

Drug interactions

- AchE inhibitors
- Aminoglycosides (Antibiotics)
- CCB Calcium channel Blockers