Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 18

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SHEET ■

SLIDES □

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CHOLINOCEPTOR BLOCKING DRUGS

Student asked: Are Muscarine and Nicotine neurotransmitters ?

They are NOT neurotransmitters, they are naturally occurring compounds present in plants and they are NOT present inside the body normally, unless you ate poisonous mushroom so you will get muscarine or you inhaled smoke so you will get nicotine. Then muscarine binds to muscarinic receptors and nicotine binds to nicotinic receptors, because we have cholinergic receptors (muscarinic and nicotinic receptors).

Note

Cholinergic receptors (muscarinic and nicotinic) are found in our body in order to bind Ach. But when we take muscarine it will bind to muscarinic receptors and when we take nicotine it will bind to nicotinic receptors.

Cholinoceptor-blocking drugs

-What do we mean by cholinergic blocking drugs?

Drugs that block cholinergic receptors.

-What do we mean by blocking?

Inhibiting or preventing the action of cholinergic receptors.

-What kind of cholinergic receptors do we have?

Muscarinic and nicotinic receptors.

-Where are the nicotinic receptors located?

Neuromuscular junctions and autonomic ganglia.

-Where the muscarinic receptors are located?

Post-ganglionic neurons (in the synapse between the post-ganglionic neuron and the effector organ) we have both post synaptic receptors and presynaptic autoreceptors.

So, cholinoceptor blocking drugs contain 3 types:

1- Antimuscarinic drugs.
2- Ganglion blocking drugs: that block nicotinic receptors in the ganglion or in the ganglia.

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3- Neuromuscular junction blockers: that block nicotinic receptors at neuromuscular junction. (this is NOT autonomic nervous system, so we are not going to talk about it today, that will be given in systems (skin and musculoskeletal system)).

Ganglion blocking drugs: they block nicotinic receptors in the ganglion and they don't have any therapeutic value now (we aren't going to talk about them now). But there are a lot of ganglion blocking drugs that were used before for treatment of hypertension, these aren't available anymore because there are better drugs.

So, this lecture will be concerned with antimuscarinic drugs(drugs that block muscarinic receptors) only.

So, antimuscarinic drugs are called muscainic receptors blockers and can also be called parasympatholytic agents which means inhibitors of parasympathetic nervous system (the doctor doesn't like this name because it's NOT specific, these drugs also affect autonomic ganglia and you don't want that).

So, the correct description of these drugs is antimuscarinic drugs or muscarinic receptor blockers. ☺

Antimuscarinic drugs

They include but NOT limited to:

1-**Naturally occurring compounds**: they are present in our environment especially in in certain plants.

-These drugs, the prototype of them is Atropine , what do we mean by **prototype**?

The representative of these compounds is Atropine (الممثل الشرعي) .

Atropine is the first drug discovered then semi synthetic and synthetic drugs came after that.

- **Semi synthetic drugs: modification** of natural compounds in the chemical laboratory to have a particular characteristics .

- **Synthetic drugs: completely** synthesized in the lab, they're NOT produced by modification of the natural compounds.

Atropine (hyoscamine) and scopolamine (hyoscine) are the naturally occurring compounds. (the doctor won't ask us about the names in brackets, but if you read them in books this is what they mean) ☺.

2-**Tertiary amines** for peripheral applications. These are semi-synthetic and synthetic compounds:

-Pirenzepine for peptic ulcer disease , it is selective for gastric acid secreting cells, while atropine and scopolamine are NOT selective; they (atropine and scopolamine) will block all muscarinic receptors in the body that they come in contact with since they are lipid soluble so they will also block muscarinic receptors in the brain.

-Tropicamide is selective for receptors in the Iris (in the circular muscle of the Iris) and it produces dilation of the **pupil** (mydriasis).

We call drugs that cause mydriasis-→ mydriatics.

3-**Queternary ammonium** for uses in bronchial asthma. Ipratropium bromide, it is semisynthetic coming from atropine . They give it by inhalation so it will dilate the bronchial tree and reduce the secretions.

Some plants that produce atropine and scopolamine for toxicological purposes Not for Fun ☺ . When you will become a Doctor enshAllah ☺ and when you work in the emergency room, you will see children coming with poisoning from atropine-like drugs ,why?! Because they were in the wild and picked some plants and ate them. Even adults can do that and NOT only children !

If you look at the source of atropine (for sure, there are different sources for atropine more than two, but the doctor put here only two):

1- **Atropa belladonna** (Latin name of certain plant)
Belladonna means beautiful (الحسناء) , before in Arabian world when Ibn sina and al-Razi were alive, they were calling this plant (حشيشة ست الحسن) why?! Because at that time, girls were trying to become beautiful by putting Atropa belladonna's juice in their eyes to dilate their pupils → girls will be prettier (as they thought) but in fact they became blind *.* how? Normal dilation of our eyes is enough to allow proper amount of light to pass trough so we can see each other clearly, **dilation** of the pupil allows **more** light to pass through so we can't see. **Constriction** of the pupil lets small amount of light to pass through so we can't see clearly either → so **normal dilation** of the pupil is the most suitable form that allows us to see each other clearly ☺

Note: in darkness: dilation of the pupil will occur.

In light: constriction of the pupil will occur.

So the opening of the pupil is just enough to allow proper amount of light to pass through so you can see ☺

2- Datura Stramonium Or Jimson weed.
It can produce Atropine.

Source of scopolamine:

Hyoscyamus niger or henbane.

The other drugs are either semi-synthetic or fully synthetic.

Lets take a look at **Atropa Belladonna** :

Notice its fruits, black in color, attractive to the children and to the adults with half knowledge :P(all colorful fruit have antioxidants as well as Atropine), if you eat more of this plant, more atropine will enter to your body, atropine is lipid soluble so it will enter the brain to gives us full long picture of poisoning.

This is **Datura Stramonium** which also forms Atropine

These are different stages of Datura's growth.

As you see, the shape of these plants is beautiful and highly attractive ☺

This is **Hyoscyamus niger**

Niger means black

Note:

Most ornamental (decorative) plants present in our houses are poisonous so be careful *.*

So these are some of the plants that form atropine, mainly found in rural areas. When you go to Princess Basma's Hospital in Irbid, you will see cases of mushroom poisoning and other types of poisoning.

Anti-muscarinic drugs

Pharmacokinetics

Natural compounds are lipid soluble (scopolamine and atropine) → they can cross membranes so they will be distributed all over the body including the central nervous system (when we talk about pharmacological effects, we will see CNS manifestation of these two drugs), they can be absorbed orally and so on.

Quaternary ammonium agents which are semi synthetic and synthetic agents → 10%-30% of the dose is absorbed after oral administration (notice that we didn't say 0% absorption, we said before that quaternary ammonium won't get absorbed or distributed at all , but these agents are **different** → the doctor don't know the reason of that but there's some absorption).

Scopolamine is more lipid soluble than atropine, so more of it will go to the central nervous system.

Half life of Atropine is 2 hours and the action lasts for 72 hours! How?! Meaning if you put atropine in eyes from **Atropa Belladonna,** impairment of vision will last for 72 hours and then its action will be gone once it's eliminated (reversible).

Student asked: 60% of Atropine dose is excreted unchanged in urine, does that means that it's not metabolized?

60% of Atropine dose is excreted unchanged in urine. Many drugs are both renal excreted and metabolized by kidney, that depends on their partial lipid solubility and partial water solubility. If the drug is lipid soluble then it's usually metabolized, if it's water soluble then it's usually excreted, BUT if the drug is both water and lipid soluble then part of it will be metabolized(lipid soluble), another part will be **excreted with urine**. In this case, **60%** of atropine is **eliminated** by urine while **40%** is **metabolized in kidney** (the doctor didn't mention that in the slides because usually we refer to the higher ratio) .

How do Anti-muscarinic drugs block muscarinic receptors? (the mechanism of their action)

They compete with Ach for binding to the receptor, competition between Ach and Atropine (which is the prototype).

→ if **Atropine** binds → **Ach** won't bind → you will NOT see **Ach**'s actions.

Imagine that there are two students who want to sit on the same chair, who will sit last? The longer one. Same here with competition between Ach and Atropine, the strength is measured by the concentration of these substrates (Ach and Atropine). → the one with the higher concentration → the chance of getting bound to the receptor is higher meaning that:

If Atropine concentration is higher that Acetyl choline (Ach) concentration → Atropine will bind and inhibit the action of Ach (inhibit the action of the receptor) and vice versa.

We use this property of competitive inhibition to antagonize the action of Atropine meaning: if we have excessive Atropine effect, what should we do? How can you reverse it? By increasing Ach concentration. How? We use anti-cholinesterases (drugs not the toxins).

So the mechanism of the action is competitive inhibition.

Now, what are the effects of anti-muscarinic drugs on secretions?

Do you remember what we talked about in parasympathetic stimulation effect on secretions? We said that Ach will increase the secretions in the salivary and gastric glands more that pancreatic and intestinal secretions.

In the blockers→ atropine will block salivary, bronchial and sweat glands more than acid secreting gastric cells

So acid secreting gastric cells are **least** sensitive (least sensitive doesn't mean NOT sensitive, it's sensitive to atropine but less than other gland secretions)

What will happen when Atropine inhibits salivary excretions? No saliva → dry mouth.

No lacrimation → dry eyes, how do we know that eyes are dry? You feel that there's sand in eyes but actually there's no sand present in the eyes, it's just a feeling that allows you to know that these eyes are dry.

Atropine effects on gastric acid secretions are very important, because increase in gastric acid secretions causes peptic ulcer, so we can use atropine to decrease these secretions and thus treats peptic ulcer.

Atropine blocks M1, M2 & M3 muscarinic receptors, while pirenzepine and dicyclomine block mainly M1 receptors. → here we are talking about selectivity for receptors.

You can say that atropine will block all muscarinic receptors all of them, so its action is NOT specific which means that if I want to treat peptic ulcer and I give the patient atropine → he will suffer from: vasodilatation so impairment of vision , dry mouth (no saliva), dry eyes(no lacrimation), tachycardia, constipation and many undesired effect will happen.. so?! If we want to treat peptic ulcer, we need something which is specific for gastric cells which is **pirenzepine**. So, **pirenzepine** is specific for gastric secreting cells and this is the drug that we use to treat gastric ulcer.

If I want to dilate pupils for a certain reason, usually they do that for eye examination to have more space of examination by ophthalmoscope or by slit lamp. If I used atropine for pupil dilation in this case, the patient will suffer from impairment of vision **at least** for 3 days! So we want more specific drug with shorter duration (causes dilation only during examination) such as **dicylomine** . So it's used as a mydriatic because it has shorter duration than atropine.

Note: cholinergic agents cause bradycardia so antimuscarinic drugs cause the opposite.

Organ system effects

1. **CNS**

We will compare Atropine with scopolamine because both of them can cross the blood brain barrier (scopolamine more than atropine because it's more lipid soluble).

a. Atropine has minimal stimulant effect on parasympathetic medullary centers (part of the CNS found in the cranium before the spinal cord), if you block muscarinic receptors there → will cause small stimulation of parasympathetic medullary centers that is at the beginning. That will be followed by: slower, longer acting

sedative effect on the brain, what do we mean by sedative effect? Calm effect (it's the first stage of sleeping then drowsiness (half awake and half sleep) then sleep will occur. Atropine causes sedation (the patient will be more calm).

b. Scopolamine causes drowsiness (half sleep and half awake).

→ if you give him higher dose→ sleep will occur → increase the dose further → comatose(coma) will occur .

➔ Normal dose (intermediate dose) → drowsiness (half awake and half sleep) → these types of people can't work, drive a car even ride a horse → then amnesia will occur

What is amnesia? Its memory loss but in this case its temporarily. Why is is important? It's important in anesthesia. Anesthesiologists love amnesia.

Meaning: the patient has a sugary and he is afraid → he needs sedation → Anesthesiologist will give him pre-anesthetic medication (scopolamine or atropine). One of the functions of these pre-anesthetic medication - mainly scopolamine - is producing amnesia: first it produces sedation (the patient will be calm , NOT afraid. At the same time, the patient will go into amnesia before and for a while after the surgery , so the patient will be calm and relaxed all the time. When amnesia is gone the surgeon tell the patient that everything is okay ☺ he will be relaxed.

Amnesia is also used by Gynecologist specially during delivery where the mother is suffering from severe pain :/ they give her a drug other than scopolamine that causes amnesia. Amnesia in this case allows the mother to sleep without affecting uterine contractions so the mother will deliver the baby by normal vaginal delivery→after the delivery, the nurses will come up to here congratulating her saying you have got a baby, and the mother will say: Oh, I have got a baby?!!!! :O

Notes:

-There are many pre-anesthetic medications other than scopolamine such as Benzodiazepine (it will cause amnesia).

- We give only **one dose** of Pre- anesthetic medication, NOT continuous doses, so if it has any side effects, they won't last for long unless the side effect is severe.

- If the pre-anesthetic drug has any bad effect on uterine contractility, the delivery or the fetus, we shouldn't give it.

- We give these medications IV.

- If I don't get any drugs that affect the ANS, I will act normally but if I get a drug like atropine (its concentration is higher than that of Ach) it will inhibit muscarinic receptors and I will have manifestations (we

talked about these manifestations in the CNS, when we can use them and they can be dangerous in some patients).

-anti-histamines that we take in allergy are anti-cholinergic property, they advised the patient who take these drugs: Don't drive a car! You will hurt yourself because you are in a partial sleep state. This is due to anti- muscarinic effects of these drugs.

-normal (regular) dose of atropine causes sedation , normal (regular) dose of scopolamine causes drowsiness and amnesia, but toxic doses of atropine can produce these (drowsiness and amnesia) but it's NOT like hypnotics.

Student asked: is there a way to get the same effect of anti-muscarinic drugs by using sympathetic agonists?

No one like this type of treatment, because the sympathetic and parasympathetic effects are **not always** opposite to each other, even though they have **certain** effects opposite to each other. So, sympathetic agonists won't make anti- muscarinic drug effects.

We talked about the anti-muscarinic effects for anti-muscarinic drugs that can cross the blood brain barrier. These effects are at **regular doses** (**therapeutic doses**).

High doses (not toxic ones) of scopolamine may lead to coma and death.

At **toxic doses**, both can produce excitement, agitation, hallucinations and coma.

What is excitement? تهيج

What is agitation? Become restless (restlessness).

What is hallucination? False perceptions meaning they perceive non-**existing** things (the patient said: there's a plane F15 in this room!!). It's not only visual perceptions. The patient may **hear** something non-existing , or he may feel that there's someone who wants to kill him or he may **smell** non-existing things.

At **therapeutic doses**, centrally acting anti-muscarinic drugs reduce the tremor of Parkinson's disease (there's an entire lecture about Parkinson's disease, so we will discuss it later on).

-Prevention or reversal of the vestibular disturbances of motion sickness – Scopolamine**.**

What is motion sickness? When you are in plane, or ship or bus you may suffer from dizziness which is caused by problems in the vestibular system inside the ears (ears are not only for hearing but also for balance).

These vestibular disturbances can be prevented and treated by Scopolamine, there are trans-dermal patches, they put scopolamine on patches then stick them on the skin before traveling (preventive use) and we can use scopolamine as treatment .because scopolamine is lipid soluble it can pass through the skin and produce its effect.

Also, scopolamine can be given as tablets (oral route).

2. Eye

a. Dilation of the pupil (mydriasis) due to block of the pupillary constrictor muscle (circular muscle of the Iris).
b. Weakens contraction of the ciliary muscle (cycloplegia) leading to loss of the ability to accommodate for near vision so failure to read a book.

Cycloplegia means **temporary** paralysis of the ciliary muscle.

c. Reduction of lacrimal secretions leading to dry or sandy eyes (caused by dry eyes).

3. Cardiovascular system (CVS)

We said that Ach causes vasodilatation, Atropine can block that.

Ach causes bradycardia so atropine can cause tachycardia **BUT Small doses** of atropine produce **bradycardia** through **stimulation** (Not blocking) of acetylcholine release by **blocking presynaptic M1 autoreceptors**.

Meaning that: in the beginning we gave the patient small dose of Atropine → auto receptors affected first and they are **blocked** → increases Ach concentration → bradycardia → after that tachycardia will happen (which is the theme that you expect from atropine). This is called biphasic conditions.

Patient may come with all signs and symptoms of atropine poisoning (pupil dilation, dry mouth..) but he has bradycardia! Due to blocking presynaptic autoreceptors and for sure, this will be followed by tachycardia which is the theme that you expect for atropine.

The same mechanism operates in the AV node (enhances conduction).

Vasodilatation (caused by Ach) is blocked by atropine BUT atropine itself is a vasodilator but with an unknown mechanism! So toxicity of atropine is manifested in part by flushing of the face, it's NOT related to muscarinic receptors and we don't know it's mechanism BUT it's very important.

So, if a patient came with all symptoms and signs of atropine poisoning and flushy face, be sure that he has atropine poisoning because atropine causes vasodilation of skin blood vessels by unknown mechanism BUT it's NOT related to muscarinic receptors or Ach.

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Remember this quote: "life is just like a camera, click, continue and smile, NEVER give up and cry" Be optimistic ☺