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Pharmacology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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In the previous lecture we discussed anticholinesterase drugs, and what they are used for.

- ✓ **Alzheimer's disease:**
  In people with advanced Alzheimer's disease, certain neurons are much less active and thus longer time is required for brain signals to be sent ***(Deficiency in cholinergic transmission)*****.**
- ✓ ***Treatment?***
  There is no cure for Alzheimer's, but some medications aim to relieve the symptoms and slow down the progression of the disease like ***anticholinesterases (special ones):***

Tacrine	is an anticholinesterase used for the treatment of mild to moderate Alzheimer's disease. But Tacrine's efficacy is **modest**, and **hepatic toxicity** is significant.
Donepezil	is **newer, more selective and it's** used in treatment of cognitive dysfunction in Alzheimer's patients. Given once daily because of its **long half-life**, and it **lacks the hepatotoxic effect of tacrine. Better drug to treat Alzheimer's.**

Toxicity of cholinesterase inhibitors:

- ✓ Varies markedly depending on their absorption, access to the CNS, and metabolism.
- ✓ Lipid soluble compounds like organophosphates are absorbed very well even by the skin, and can get into the brain (penetrate the **B**lood **B**rain **B**arrier).
- ✓ ***Pilocarpine*** and ***choline esters*** over dosage causes muscarinic actions:
  Enhances the activity of the GIT causing (nausea, vomiting, diarrhea), urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction.
- ✓ All secretions are increased.
- ✓ All of the previous effects are blocked competitively by ***atropine.***

Muscarine poisoning:

- ✓ contains muscarinic alkaloids.
- ✓ (**Amanita muscaria**, the first source of muscarine, contains very low concentrations of the alkaloid.)
- ✓ Ingestion of these mushrooms causes typical signs of muscarinic excess within 15–30 minutes.
- ✓ **TREATMENT: Atropine blocks the effect of Ach at muscarinic receptors but does not affect nicotinic receptors.**
- ✓ Atropine is given parenterally, (delivered by routes other than the GI tract, usually administered by injections) **1–2 mg** .

Nicotinic Stimulants-Acute Toxicity:

- ✓ Nicotine is very poisonous, the fatal dose of nicotine is **40 mg, or 1 drop** of the pure liquid; this is the amount of nicotine in two regular cigarettes.
- ✓ **It is not likely that someone will overdose on nicotine just from smoking cigarettes, why?**

  Fortunately, most of the nicotine in cigarettes is destroyed by **burning** or escapes via the **"side stream" smoke**.

Toxic effects of a large dose of nicotine are:
central stimulant actions, which cause **convulsions** and may progress to **coma** and **respiratory arrest**.
skeletal muscle **end plate depolarization**, which may lead to a **depolarization blockade and respiratory paralysis.** **What is a depolarization block? (just for clarification)** When cholinergic sites (nicotinic ones in this case) undergo prolonged depolarization, the voltage gated Na+ channels are trapped in their inactivated state. Their activation gates remain open and their inactivation gates remain closed, so they are in their **closed and not capable of opening conformation.** This depolarization prevents the initiation of a new action potential,the most harmful result is respiratory failure due to failure of diaphragm contraction. Consequently, the person cannot breathe.
hypertension and cardiac arrhythmias.

- ✓ Children and infants might ingest nicotine, insecticides or tobacco. Fortunately this is usually followed by **vomiting**, limiting the amount of the alkaloid absorbed and eliminating most of the ingested nicotine.

- ✓ **Treatment?**

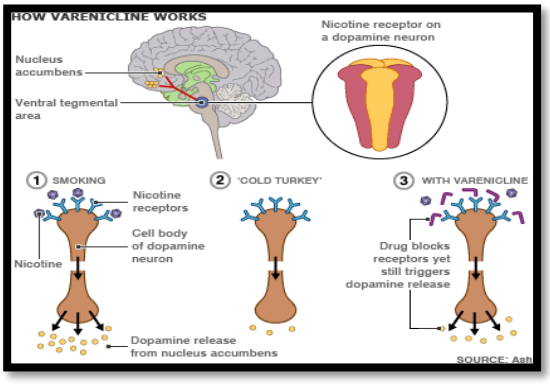
  Treatment of acute poisoning is **symptom-directed** (therapeutic management of the symptoms that arise due to a given disease).

  1. Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with **atropine**.
  2. Central stimulation is treated with anticonvulsants such as **diazepam**.
  3. Neuromuscular blockade is not responsive to treatment and requires **mechanical respiration** (patient is placed on a ventilator).

- ✓ Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first **4 hours** usually recover completely if hypoxia and brain damage have not occurred.
- ✓ **Chronic Nicotine Toxicity:**

  Nicotine contributes to an increased risk of vascular disease and sudden **coronary death** associated with **smoking**. Also, there is a high incidence of **ulcer recurrences in smokers.**

- ✓ Replacement therapy with nicotine in the form of **gum, transdermal patches, nasal spray, or an inhaler** are used to help patients stop smoking.
- ✓ **Varenicline in nicotinic replacement therapy:**
- ✓ Is a drug used to treat smoking addiction, it has partial agonist action at central nicotinic receptors. As a result, it reduces cravings for cigarettes and decreases its pleasurable effects.
- ✓ It also has antagonist properties (remember that partial agonists act as competitive antagonists) that persist because of **its long half-life.**



- ✓ **Mechanism of action:**

  It is a high affinity partial agonist for nicotinic receptors. A competitive binding reduces the ability of nicotine to bind and release dopamine with full agonism, varenicline releases dopamine in the nucleus accumbens (where dopamine is released - pleasure center) and therefore has the capacity to reduce cravings for cigarettes.

- ✓ It prevents the stimulant effect of nicotine at presynaptic nicotinic receptors that cause release of dopamine, so smoking will no longer satisfy individuals because receptors are blocked by the partial agonist.
- ✓ **SIDE EEFECTS:**

  Nausea and **insomnia** and **exacerbation** (the worsening of a disease or an increase in its symptoms) **of psychiatric illnesses**, including **anxiety** and **depression**.
- ✓ **Cholinesterase Inhibitors:**
- ✓ The major source of intoxication is **Pesticides**.
- ✓ **Organophosphates** are a group of chemicals that **irreversibly inhibit AChE**, preventing inactivation of Ach. Death from organophosphates is also due to **respiratory failure** because the diaphragm cannot repolarize and return to resting conditions, then contract again. These toxic agents are used in some **pesticides** and **military nerve gases (soman, sarin, VX)** which induce effects rapidly and cause symptoms which persist for days.
- ✓ Organophosphate intoxication leads to **muscarinic affects:**

  Miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea. CNS involvement (**cognitive disturbances, convulsions, and coma**) usually follows rapidly, accompanied by peripheral nicotinic effects, especially '**depolarizing neuromuscular blockade'.**
- ✓ Exposure to nerve agents like Sarin is lethal even at low concentrations, death can occur within minutes after direct inhalation because **aging occurs rapidly** when the inhibitor is a powerful nerve agent.
- ✓ **Treatment:**

  (1) maintenance of vital signs—respiration in particular may be impaired (**mechanical respiration).**

  (2**) decontamination** to prevent further absorption, washing hands and clothes to prevent further absorption.

  (3) **Atropine parenterally in large doses** given as often as required to control muscarinic excess, until heart rate is increased and pupil dilation (mydriasis) is observed.
- ✓ Therapy often includes treatment with **pralidoxime**, and **benzodiazepines** for seizures.

- ✓ **Preventive therapy for cholinesterase inhibitors warfare agents:** Personnel who are likely to be attacked with chemical weapons often carry auto injection syringes containing **pyridostigmine (reversible anticholinesterase, anti-nerve agent)** and **Atropine** to reduce the effect of nerve gases (if inhaled) by blocking muscarinic receptors.
- ✓ **You might wonder, why do we use AChE inhibitor as a preventive therapy against exposure to nerve gases, which are basically AChE inhibitors?**

Pyridostigmine is a **reversible AChE inhibitor** used for protection against exposure to anticholinesterase nerve agents (e.g., sarin). Because pyridostigmine has a **much shorter duration of inhibition**, **and does not "age"** (as possible with many organophosphorus anticholinesterases). The relatively short-term inhibition of some proportion of acetylcholinesterase molecules by pyridostigmine **can protect those enzymes** from the much longer inhibition caused by exposure to an irreversible organophosphorus agent. The enzyme is basically protected by being occupied by a much less harmful drug than organophosphate compounds.

- ✓ **Chronic exposure** to certain organophosphate compounds causes **delayed neuropathy associated with demyelination of axons, by two types that both produce muscle weakness.**

First type appears 1–2 weeks after exposure. The effects are not caused by cholinesterase inhibition but rather by **neuropathy target esterase (NTE) inhibition whose symptoms** (weakness of upper and lower extremities, unsteady gait).	Second type of nerve toxicity is called **intermediate syndrome** and it **occurs 1–4 days after exposure to organophosphate insecticides**. This syndrome is also characterized by **muscle weakness**; its origin is not known but it appears to be related to cholinesterase inhibition.

Cholinoceptors-Blocking drugs (antimuscarinic-sympathomimetics):

Drugs that block muscarinic cholinoceptors. Five subtypes of muscarinic receptors, all present in CNS :
M1 sympathetic postganglionic cell bodies, and many **presynaptic sites**.
M2 in the **myocardium**, smooth muscle organs, and some neuronal sites.
M3 on effector cell membranes, especially **glandular** and **smooth muscle** cells.
M4 and **M5** play a greater role in the **CNS** than in the periphery.

Absorption:

- ✓ **Natural alkaloids** (Solanaceae species,e.g. **atropa belladona**) & most **tertiary antimuscarinic drugs are well absorbed.**
- ✓ **Scopolamine (hyoscine)** is absorbed across the skin (transdermal).
- ✓ **Quaternary antimuscarinic** drugs 10–30% of a dose is absorbed after oral administration
- ✓ Tertiary amines are more toxic than quaternary drugs because they are easily absorbed and well distributed.

Distribution:

- ✓ **Atropine** and the other **tertiary agents** are widely distributed, they reach the CNS within 30 minutes to 1 hour.
- ✓ **Scopolamine** is rapidly and fully distributed into the **CNS where it has greater effects than most other antimuscarinic drugs.**
- ✓ In contrast, the **quaternary derivatives** are poorly taken up by the brain.

Metabolism and Excretion:

Elimination of atropine occurs in two phases:

1. The t1/2 of the **rapid phase** is **2 hours**.
2. The t1/2 of the **slow phase** is **13 hours**.

Why is that?

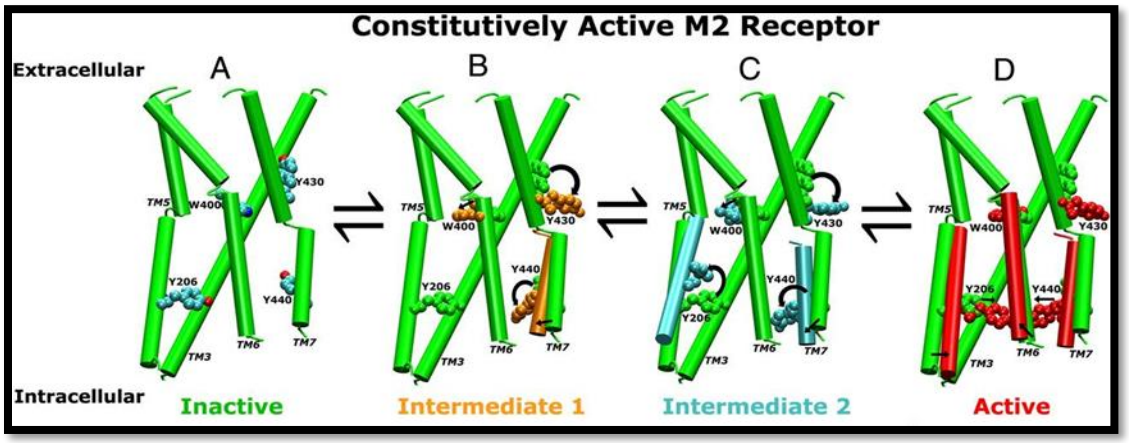
Atropine is an **enantiomeric (racemic) mixture** of D-hyoscyamine and L-hyoscyamine, with most of its physiological effects due to **L-hyoscyamine that has a short half-life.** About 50% of the dose is excreted unchanged in the urine (the **dextro form is not metabolized** by the body).

- ✓ Most of the rest appears in the urine as hydrolysis and conjugation products.
- ✓ The drug's effect on parasympathetic function declines rapidly in all organs **except the eye.**
- ✓ Effects on the iris & ciliary muscle persist for **72 hours.**

Mechanism of Action:

Atropine causes reversible blockade of all M receptors.

- ✓ Muscarinic receptors are **constitutively active (A receptor which is capable of producing a biological response in the absence of a bound ligand, that is the receptor is partially activated without its ligand).** Muscarinic blockers are **inverse agonists** that shift the equilibrium to the **inactive state** of the receptor, while full agonists shift the equilibrium to the **active state**.



- ✓ Tissues most sensitive to atropine are the **salivary, bronchial, and sweat glands.**
- ✓ **Secretion of acid** by the gastric parietal cells is the **least sensitive**.
- ✓ Antimuscarinic agents **block exogenous cholinoceptor agonists more effectively than endogenous agonists** (it is not easy to block the receptor when Ach is being released closely and thus binds quickly to its receptor, but it is easier to block circulating muscarinic drugs, which need more time to reach their receptors and bind to them).

Organ System Effects:

- ✓ **Atropine** has minimal stimulant effects on CNS.
- ✓ **Scopolamine** has more marked central effects, producing drowsiness and amnesia.
- ✓ In toxic doses, scopolamine, and atropine, can cause excitement, agitation, hallucinations, and coma.

The tremor of Parkinson's disease:

There is no cure for the disease itself, but medications can help to control the symptoms.

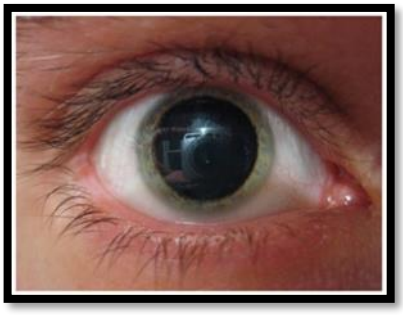
Parkinson's is caused by an imbalance between cholinergic activity and dopaminergic activity in the brain. Dopamine levels are reduced which ultimately leads to the symptoms of Parkinson's disease like tremor. The primary treatments for PD are **Dopamine agonists** which act directly on the dopamine receptors and mimic dopamine's effect but it is believed that by **blocking Ach receptors, anticholinergics can treat the symptoms -particularly the tremor that is characteristic of PD.**

- ✓ The tremor of Parkinson's disease is reduced by centrally acting **antimuscarinic drugs**, and **atropine**—in the form of belladonna extract—was one of the first drugs used in the therapy of this disease.

Vestibular disturbances - Sea-sickness:

Scopolamine is effective in preventing or reversing these disturbances.

Eye:



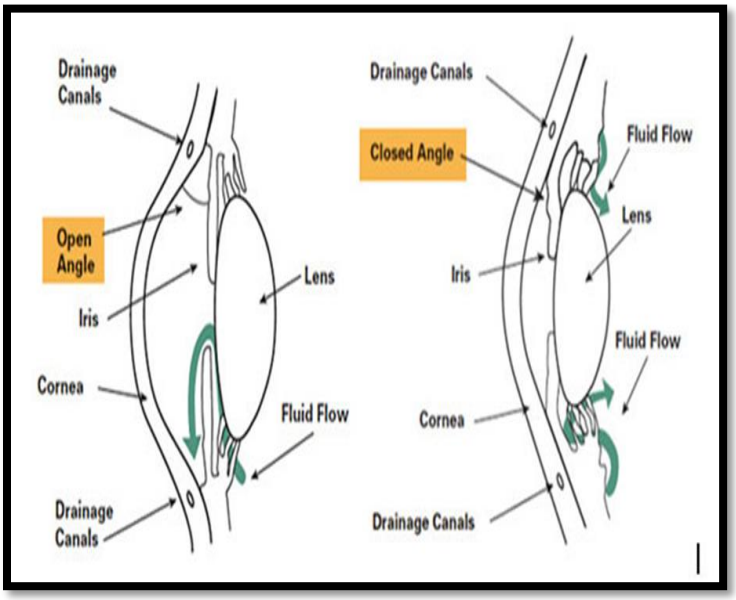
Atropine and other **tertiary antimuscarinic** drugs cause an unopposed **sympathetic dilator activity and passive mydriasis.**

Paralysis of the ciliary muscle, or **cycloplegia (far-vision focus)** results in loss of accommodation; the fully atropinized eye **cannot focus for near vision**.

Active mydriasis: by **stimulating α1-adrenergic receptors in the dilator pupillae muscle.**

Passive mydriasis: induced by atropine and antimuscarinic drugs by **blocking contraction of the circular pupillary sphincter muscle.**

- ✓ Cause acute glaucoma in patients with a narrow anterior chamber angle.
- ✓ Antimuscarinic drugs reduce lacrimal secretion causing **dry or "sandy" eyes**.
- ✓ Antimuscarinic drugs such as atropine are **contraindicated** in angle-closure glaucoma because of the increased likelihood of producing complete obstruction of the outflow of aqueous humor, **resulting in an acute increase in intraocular pressure (IOP).**

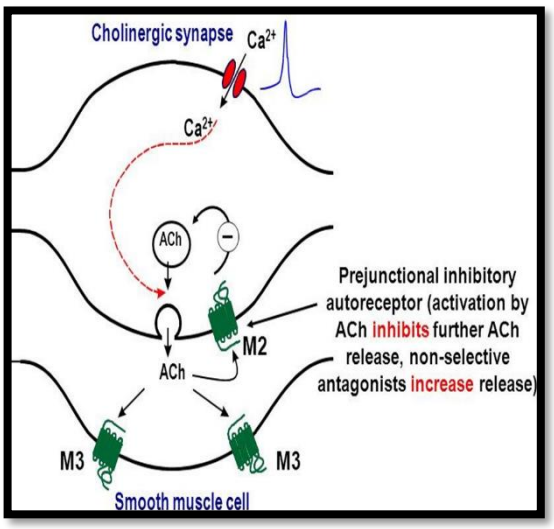


Cardiovascular System:

- ✓ Atropine causes **tachycardia by vagal block (block of M2 receptors).**
- ✓ Lower doses often result in **initial bradycardia** before the effects of peripheral vagal block is seen.
- ✓ This slowing may be due to blockage of **M1 autoreceptors** (that stop the release of Ach) on vagal postganglionic fibers.
- ✓ Presynaptic receptors are always more sensitive than postsynaptic receptors. Small doses can easily block these receptors.
- ✓ The ventricles are less affected. In toxic concentrations, it can cause an intraventricular conduction block due to local anesthetic action.
- ✓ All blood vessels contain endothelial **M3** receptors that mediate **vasodilation.**

These receptors are blocked by antimuscarinic drugs. At toxic doses antimuscarinic agents cause cutaneous vasodilation, especially in the the **blush area**. The mechanism is unknown (thank God).

Respiratory System:



- ✓ The effectiveness of nonselective antimuscarinic drugs in treating bronchial asthma is limited. **Blockage of autoinhibitory M2 (more Ach is released as a result) opposes the bronchodilation caused by blockage of M3 receptors in the airway.** Competitive binding between atropine and Ach on muscarinic receptors would occur reducing the antimuscarinic effect of atropine.
- ✓ Atropine causes some **bronchodilation** and **reduces secretion**.
- ✓ Doctors use **Antimuscarinic drugs** before the administration of **inhalant anesthetics** to suppress salivary and bronchial secretions before surgery, to reduce the risk of a patient inhaling these secretions into the lungs.

Gastrointestinal Tract:

- ✓ Complete muscarinic block cannot totally abolish activity of GIT, since local hormones in the enteric nervous system also modulate GI functions.
- ✓ Antimuscarinic drugs have marked effects on salivary secretion causing **dry mouth.**
- ✓ Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced but large doses of atropine may be required.
- ✓ Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.
- ✓ Atropine might delay the absorption of other drugs given orally, by inhibiting gastrointestinal motility and delaying gastric empty.
- ✓ M1 blockers like **Pirenzepine** and *telenzepine*reduce gastric acid secretion with fewer adverse effects than atropine.
- ✓ GI smooth muscle motility is affected from the stomach to the colon; both tone and propulsive movements are diminished.
- ✓ Gastric emptying time is prolonged, and intestinal transit time is lengthened.
- ✓ Diarrhea due to overdosage with muscarinic agents is readily stopped.
- ✓ Diarrhea caused by non-autonomic agents can be temporarily controlled.

Antimuscarinic toxicity can be summarized by the following phrases:

1. **Blind as a bat**

   The eye is fixed for far vision due to paralysis of the ciliary muscles (cycloplegia) which controls the shape of the lens.

2. **Mad as a hatter**

   Central excitation, resulting in restlessness, irritability, disorientation, hallucinations and/or delirium

3. **Dry as a bone**

   Antimuscarinics decrease secretions & salivation.

4. **Hot as hell**

   A decreased ability to sweat interferes with thermo-regulation.

5. **Red as a beet**

   Cutaneous vasodilation occurs in response to increased body temperature.

6. **Full as a flask**

   Interference with the contraction of bladder muscle can cause urinary retention.

Good luck ❤