PHARMACOLOGY

3 & 4: cholinergic agonists

Lecture 3 : Direct -acting cholinergic agonists

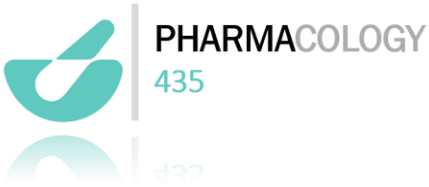
OBJECTIVE:

- To identify the mechanism of action of direct acting acetylcholine receptor stimulants
- To discuss the pharmacokinetic aspects and pharmacodynamics effects of direct cholinomimetics
- To outline the therapeutic uses and toxicity of direct cholinergic agonists

Lecture 4 : Indirect -acting cholinergic agonists

OBJECTIVES:

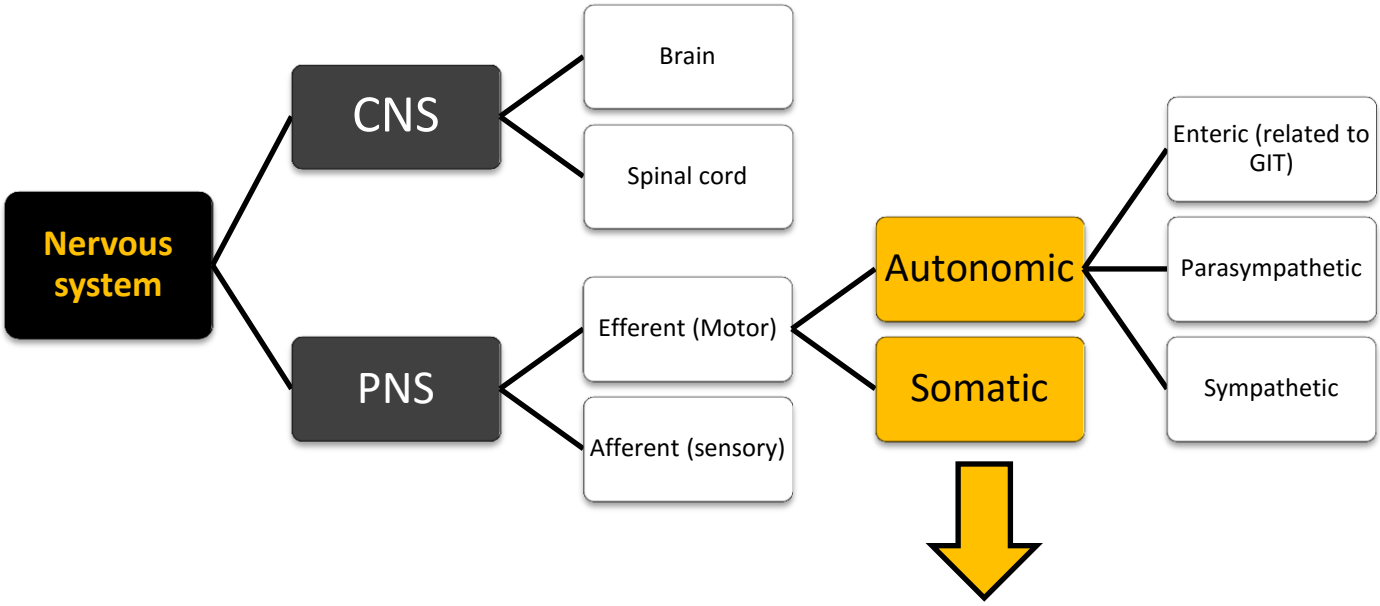
- Classification of indirect acting cholinomimetics
- Mechanism of action, kinetics, dynamics and uses of anticholinesterases
- Adverse effects & contraindications of anticholinesterases
- Symptoms and treatment of organophosphates toxicity.



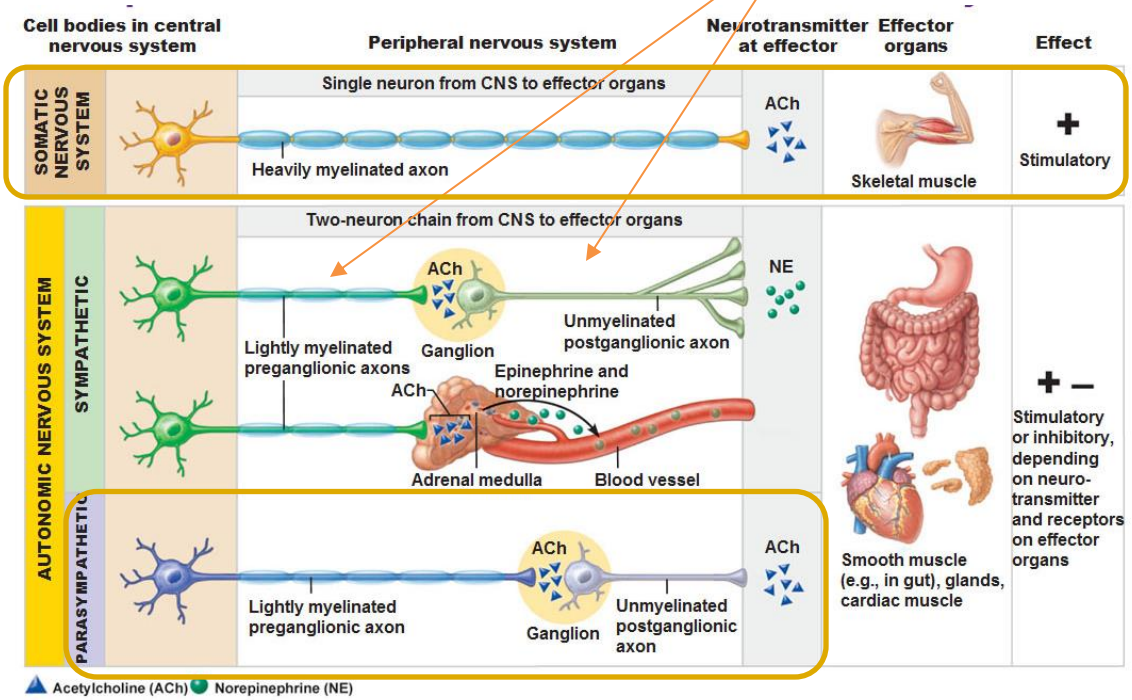
Before studying these two lectures, we advise you to take a look at lecture 6 in physiology: neuromuscular junction

- Important.
- Extra notes.

Introduction to cholinergic system



Somatic*	VS	Autonomic
Controls skeletal muscles		Controls internal viscera
Voluntary		Involuntary
One fiber nerve *soma=body		**Two** fiber nerve (Pre & Post ganglionic)



Introduction to cholinergic system

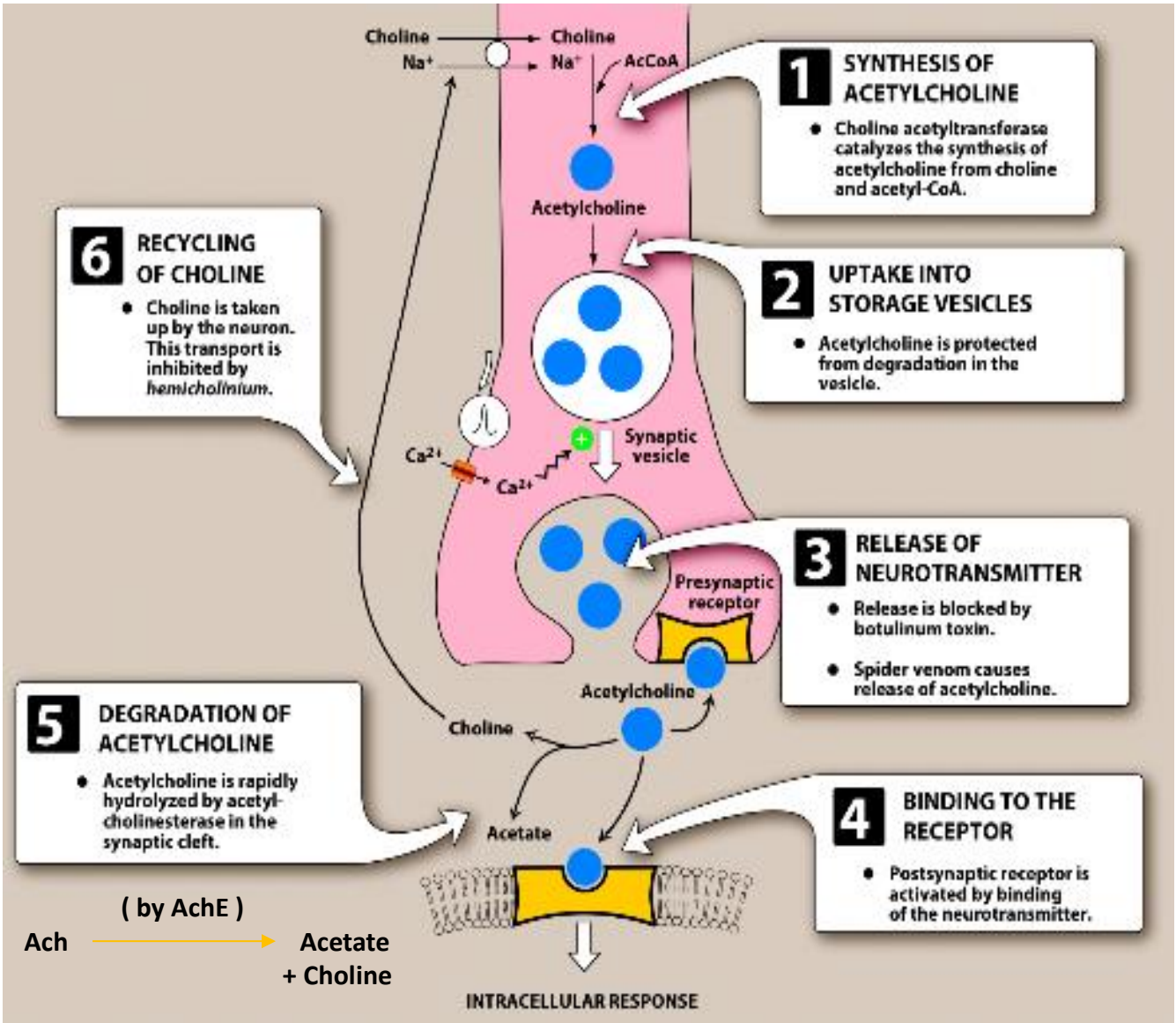
❖ Overview:

Drugs that affect the ANS are divided into two groups:

1. **Cholinergic Drugs** which act on **muscarinic and nicotinic receptors** that are activated by **Ach. (parasympathetic)**
2. Adrenergic Drugs which act on adrenergic alpha and beta receptors that are activated by Norepinephrine or epinephrine. (sympathetic)

❖ The Cholinergic Neuron:

- The neurotransmitter in **parasympathetic** nervous system (cholinergic system) is **Acetylcholine**, and nerves are called **cholinergic nerves.**
- Neurotransmission at Cholinergic Neurons involves six steps:



Classification of cholinergic agonists :

Cholinergic Drugs

Drugs that produce actions similar to stimulation of parasympathetic system (parasympathomimetics) or similar to Ach (Cholinomimetics) .

Direct

Produce primarily effect by binding directly to cholinergic receptors (**Muscarinic or Nicotinic or both**). Classification according to chemical structure :

Tertiary

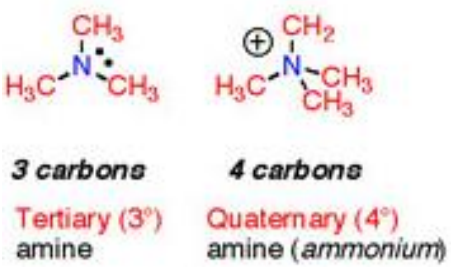
Suffix –ine = Natural alkaloids (non polar)

- **Pilocarpine**
- **Nicotine**
- **Lobeline**

Quaternary

Synthetic choline esters (polar)

- **Ach**
- **Methacholine**
  3 times more resistant to hydrolysis than Ach.
- **Cevimeline**
- **Carbachol**
  Completely resistant to AChE
- **Bethanechol**
  Completely resistant to AChE



Indirect

Act indirectly by inhibiting acetyl cholinesterase, thus prevent the hydrolysis of Ach. They are called (cholinesterase inhibitors or anticholinesterases).

Reversible

- **Edrophonium**
- **Neostigmine**
- **Physostigmine**
- **Pyridostigmine**
- **Ambenonium**
- **Donepezil**

Irreversible

Organo-phosphorus compounds:

- **Echothiophate**
- **War gases and parathion**

The Cholinergic (parasympathetic) Receptors :

Cholinergic drugs act upon two types of receptors:	
Nicotinic receptors (N) **Central cholinoreceptors**	**Muscarinic receptors (M)** **Peripheral cholinoreceptors**
Type of the receptor	
Type I: ion channel linked receptors These receptors, In addition to binding Ach, also recognize nicotine but show only a weak affinity for muscarine. Binding of two Ach cause depolarization of the effector cell.	**Type II: G-protein linked receptors** These receptors, In addition to binding Ach, also recognize muscarine (an alkaloid that is present in certain poisonous mushrooms). In contrast, the muscarinic receptors show only a weak affinity for Nicotine.
Pharmacological Action	
Almost excitatory	**Excitatory or inhibitory**
Subclasses	
Nn: at autonomic ganglia (nerves) Nm: at NMJ (muscles)	M1,M3, M5: excitatory M2,M4: inhibitory
Location and action	
Autonomic ganglia (Nn) Action: sympathetic & parasympathetic stimulation	Located at **all organs** that are innervated by **postganglionic parasympathetic** fibers (e.g, heart, CVS, eye, bladder, etc). Action: Heart → bradycardia (↓ heart rate) exocrine glands → secretion Smooth muscles → contraction **Details on the table next slide** **CNS:-** Both **muscarinic** & **nicotinic** receptors are found in the CNS
Skeletal muscles (Nm) Action: **Therapeutic dose:** Low concentration > muscle contraction **Toxic dose:** High concentration > persistent depolarization & relaxation. **NMJ is blocked by NM blockers; lecture 1**	
Adrenal medulla (Nn) Action: release of catecholamines (adrenaline & noradrenaline)	

Muscarinic receptors :

Receptor	Locations	Cholinergic pharmacological actions, Parasympathetic = rest and digest
M1 Excitatory	-CNS	– CNS excitation
	-gastric parietal cells	– Gastric acid secretion (leading to peptic ulcers)
M2 Inhibitory	-Heart endothelium	– Cardiac inhibition – Ventricle has sparse **parasympathetic** innervations. which by **reducing the force** of contraction of the atrium, cause cardiac **slowing** (Bradycardia), **↓CO** (Cardiac output), **and hypotension.** Hypotension is opposed by **reflex sympathetic** discharge.
M3 Excitatory	-Exocrine glands	- Increase of secretions of exocrine glands: sweat, saliva, lacrimal, **bronchial**, nasopharyngeal, intestinal glands .
	-Smooth muscles (GIT, urinary tract, bronchial muscles)	- Smooth muscle contraction - Increase in motility of GIT (peristalsis), thus may lead to diarrhea - Bronchospasm (may cause asthma) - Relaxation of sphincter (Urination and defecation)
	-Vascular endothelium	- Vasodilatation, this is effect not associated with muscarinic innervations, via nitric oxide (EDRF) **(Endothelium-derived relaxing factor)**
	- eye	- Contraction of circular muscle of iris (miosis) - Contraction of ciliary muscles for near vision - Decrease in intraocular pressure (IOP)
M4 & M5	-CNS	- memory, arousal, attention and analgesia

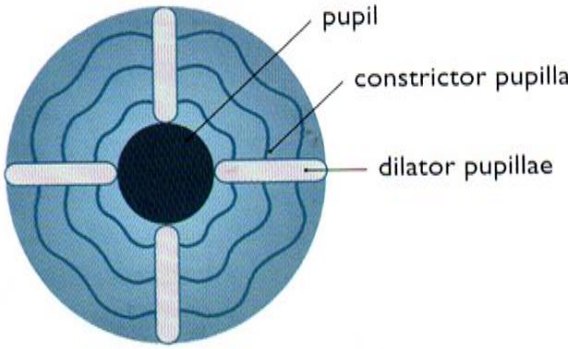
* Human uterus is **not sensitive** to muscarinic agonists.

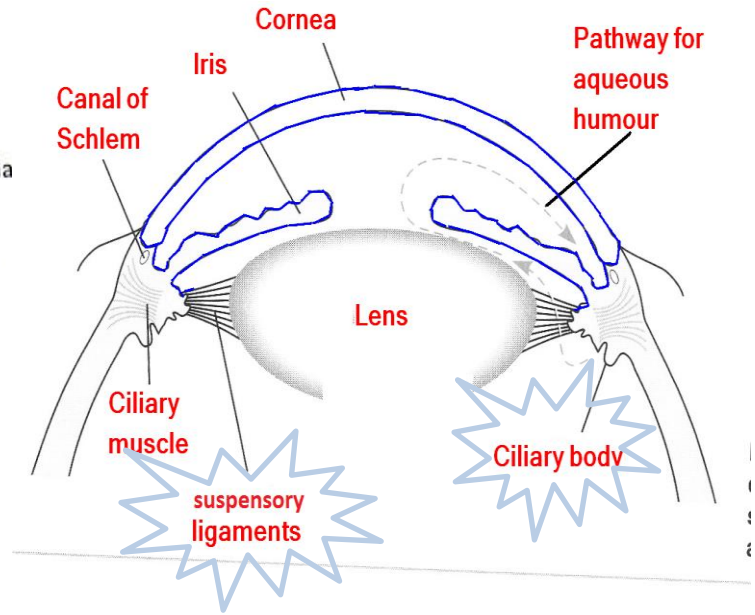
* These are the pharmacological actions for Ach, as well as direct & indirect cholinomimetics.

Pharmacodynamic Effects on the eye:

❖ The iris has two muscles that control light intensity:

1. **Dilator pupillae,** a longitudinal radial muscle which **dilates** the pupil (mydriasis) in the dark, to allow as much as possible of light to enter the eye. It is innervated by **sympathetic** NS.
2. **Constrictor pupillae,** a circular muscle which **constricts** the pupil (miosis) in places with good lighting. It is innervated by **parasympathetic** NS.





❖ Accommodating the ciliary muscle for near vision:

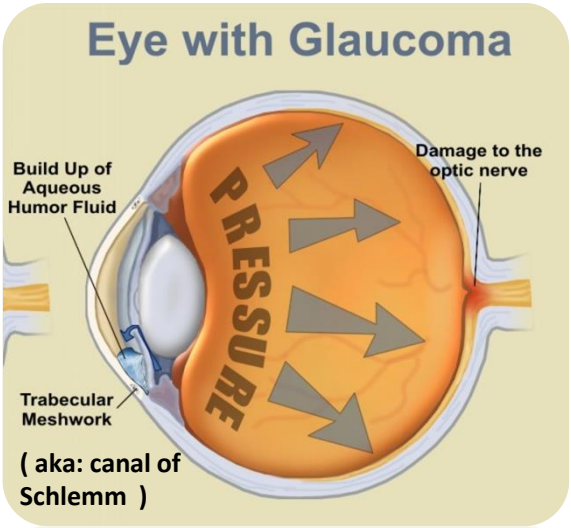
- Parasympathetic activation contracts **the ciliary muscle.** (when ACh combines with muscarinic M3 receptor).
- Contraction of ciliary muscle pulls the **ciliary body** forward & inward , relaxing **the suspensory ligaments** of the lens (lens becomes spherical).

(Contraction of ciliary body = relaxation of the suspensory ligaments , and vice versa).

- The lens bulges more (increased curvature) , this causes a decrease in focal length.
- This parasympathetic reflex is essential to accommodate for **near vision**.

ANS control of iris - University of Melbourne

Pharmacodynamic Effects on the eye (cont.)



❖ **Constrictor pupillae is important for:**

1- Adjusting the pupil in response to change in light intensity.

2- Regulating the intraocular pressure.

Regulating the intraocular pressure:

In the healthy eye:

- Aqueous humour is secreted by the cells of the epithelium covering the ciliary body.
- Increased tension in the ciliary body removes the Aqueous humour continuously by drainage into the canal of Schlemm.
- Normal intraocular pressure is 10-15mmHg above atmospheric pressure.

In some people:

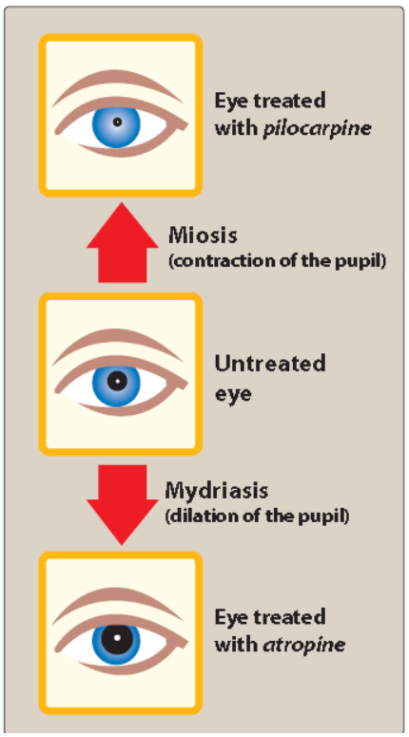
- Dilatation of their pupil will block canal of schlemm, therefore it impeds drainage of aqueous humour.
- The accumulation of aqueous humour leads to an increase in intraocular pressure.
- ↑ IOP may lead to glaucoma, and retinal detachment.

(Retinal detachment describes an emergency situation in which a critical layer of tissue (the retina) at the back of the eye pulls away from the layer of blood vessels that provides it with oxygen and nourishment).

Treatment:

When using **cholinergic drugs** (e.g. **pilocarpine**), constrictor pupillae causes miosis, which contracts the pupil away from canal of schlemm, leading to increased filtration of Aqueous humour.

Thus, activation of constrictor pupillae <u>decreases</u> intraocular pressure in patients with glaucoma.



Development of Glaucoma Animation.

Lecture 3: Direct Cholinomimetics

	Ach	Carbachol	Bethanechol	Cevimeline	Pilocarpine (Natural alkaloid)
		Synthetic choline esters			
Receptor	Muscarinic Nicotinic	Muscarinic Nicotinic	Muscarinic. methyl group, ↓potency at nicotinic.	Muscarinic (M3)	Muscarinic, mainly (M3)
Selectivity	NOT selective	Eye, GIT Urinary bladder	GIT, Urinary bladder	Exocrine glands	Mainly on eye, exocrine glands
Clinical uses	Not used clinically (proto-type)	Glaucoma	-Paralytic ileus (↓ motility of GIT) - Urinary retention	dry mouth associated with Sjogren's syndrome*	- Drug of choice in emergency Glaucoma, (by eye drops) - Xerostomia (dry mouth)
Chemistry	Quaternary Polar				Tertiary non polar
Absorption	✕	better absorbed than Ach. Muscarinic quaternary amines are less completely absorbed from the GIT but still toxic when ingested in mushroom.			Complete
Metabolism	Rapid, by Cholinesterase	NOT metabolized by cholinesterase (Resistant to hydrolysis) In Synthetic esters, that's because of the strong bond between the (choline + carbamate) instead of (acetate+ choline)			
Excretion	Excretion by **kidney**. Clearance of tertiary amines (pilocarpine) can be enhanced by **acidification of urine,** because it's an alkaline (Lipophilic)				
Duration	Very short	Long			
Administration	I.V. eye drops	Oral*, eye drops S.C.	Oral* S.C.		oral, eye drops
Further information	Because of its polarity, it is pharmacologically inactive when taken orally. It has low absorption & distribution	Cannot cross BBB (polar) Never given I.V. or I.M BUT S.C & orally . Because they cause sudden bradycardia if given by IV. * Can be given orally because they're not 100% polar		*Autoimmune disease that forms antibodies leading to dryness of mouth and eye.	Can cross BBB. (has central effects) ADRs: Sweat, Salivation, Bronchoconstriction, Diarrhea, CNS effects.

Lecture 4: Indirect Cholinomimetics (Anticholinesterases)

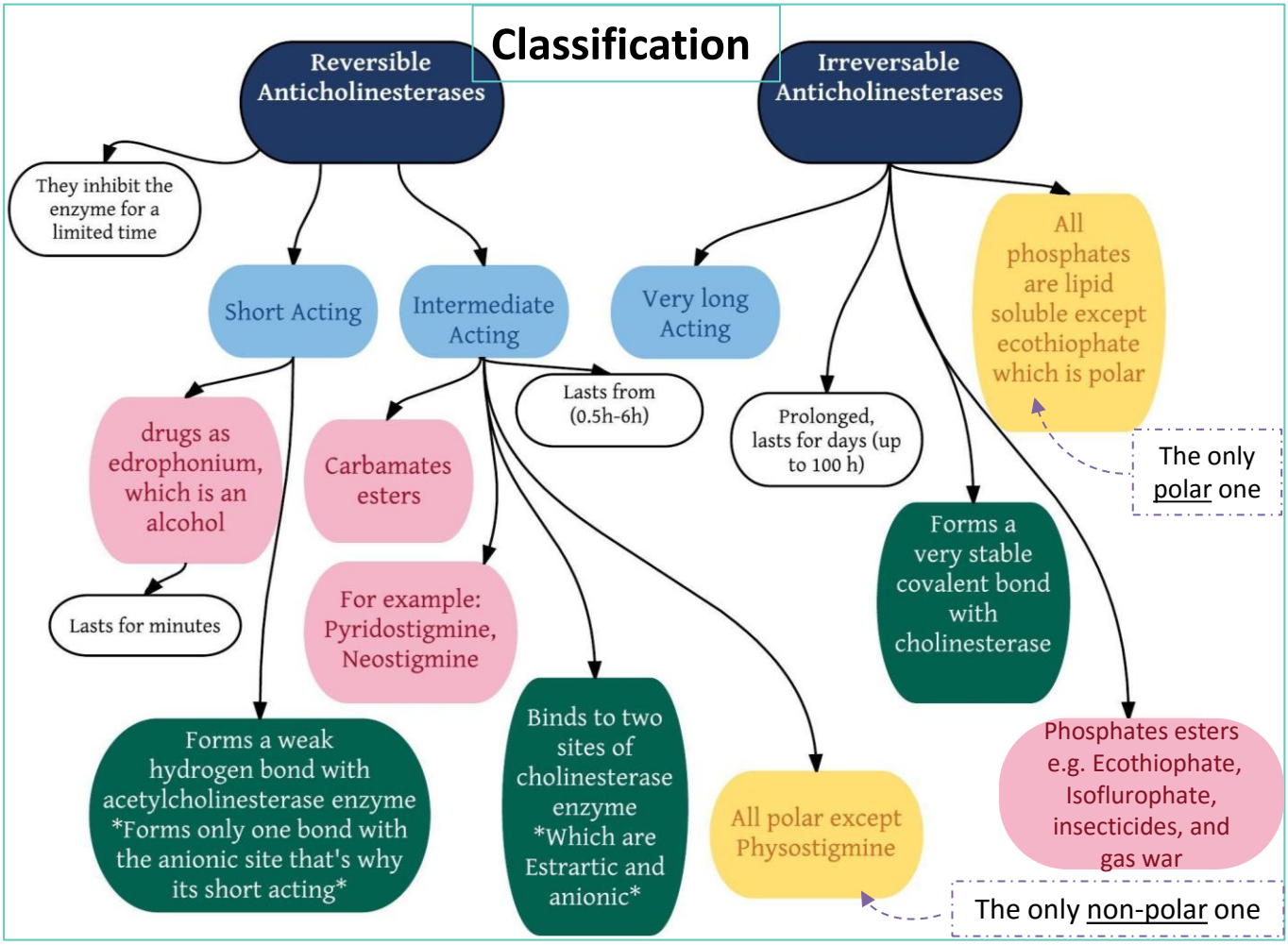
Mechanism of action:

Anticholinesterases **prevent hydrolysis of Ach** by inhibiting acetyl cholinesterase **(inhibit the inhibitor).** Those drugs inhibit cholinesterase by tricking it and combining with it **instead of Ach**, since they have **similar structure**. (any inhibiter for an enzyme must be similar in structure as the enzyme's substrate. E.g. Ach). Thus, they increase Ach concentrations and prolong its actions at the cholinergic receptors (weather nicotinic or muscarinic, since they acts on the enzyme present at the synaptic cleft of both of them).

Pharmacological effects:

All Anticholinesterases have muscarinic and nicotinic actions (N & M actions) , only lipid soluble drugs have CNS effects which can happened centrally and peripherally (excitation, convulsion, respiratory failure, coma). e.g. **physostigmine** & **phosphate ester** (except echothiophate that is polar).

Remember: Both direct and indirect cholinomimetics have pharmacological actions similar to Ach mentioned in the slides 6 & 5. (e.g. miosis, bradycardia, bronchoconstriction, increased motility, secretion of exocrine glands).



1. Reversible anticholinesterases

	Drug	Chemical structure	Administration	Kinetics	clinical Uses
Intermediate action (Carbamate esters)*	**Neostigmine**	Quaternary ammonium compound	Can be used orally but its absorption is poor (because it is ionized= polar)	- 0.5-2hr - Polar (prominent action on GIT & urinary tract).	• Myasthenia gravis treatment (nicotinic action). • Paralytic ileus (like bethanechol which is direct drug) • Urinary retention • Competitive neuromuscular blockers intoxication. E.g. Curare toxicity. Lecture 1
	Physostigmine	Tertiary ammonium compound	Good oral absorption, can be used topically in the eye	- 0.5-2hr - The only non-polar Lipid soluble	• Glaucoma • Atropine toxicity (anti-muscarinic drug) Because it is a tertiary amine (lipid soluble), **it can cross the BBB**, thus, it is used to treat the CNS effects of atropine and other anticholinergic drugs overdoses.
	Pyridostigmine & Ambenonium	Quaternary		- 3-6h & 4-8h respectively - Polar	• Myasthenia gravis treatment
Short action	**Edrophonium (simple Alcohol)**	Quaternary Forms weak hydrogen bond. (electrostatic forces)	NOT absorbed orally (given by injection, because of the high polarity)	- 5-15 min - Polar	• **Diagnosis of Myasthenia gravis**, not for the treatment. Since it has a very short duration of action.
	Donepezil		Given orally.		used for treatment of **dementia** (loss of memory) **of Alzheimer's disease**. **BUT** not the disease it self.

2. Irreversible anticholinesterases (Long acting)

Organophosphorus compounds E.g. Ecothiophate

Mechanism of action:

- Binds to cholinesterase by **strong covalent bond**.
- Thus, Hydrolysis by AChE is very slow '100 hours'
- Thus, Has a **long** duration of action.
- **Aging*** makes bond extremely stable.
- All are highly lipid soluble **except ecothiophate**.
- well absorbed from the skin, lung, gut & conjunctiva except ecothiophate (less stable in aqueous solution)
- Used only to treat **glaucoma****

* Aging: Long time exposure to organophosphates makes the covalent bond between the drug and the enzyme stronger. So when a patient is exposed to it in war gases or insecticide it's hard to treat him because it's both irreversible and time dependent.
They can be absorbed through skin, therefore it is common for farmers to get intoxicated while spraying insecticides bare footed and without precaution.
** Used rarely due to adverse effects.. But used safely in glaucoma because it has local effect when applied by eye drops.

Symptoms of Organophosphates toxicity:

intoxication symptoms are the same as the normal pharmacological actions, **BUT** exaggerated or in excess amount.

- **Severe** bradycardia, hypotension.
- Bronchospasm.
- Increase GIT motility.
  - Cramps (مغص) & diarrhea.
- CNS effects. Cross BBB, because it's lipid soluble.
  - Convulsion (تشنج), coma & respiratory failure.
- **Initial twitching** of skeletal muscles. Depolarization block
  - Muscle weakness & paralysis.

Treatment of organophosphate toxicity

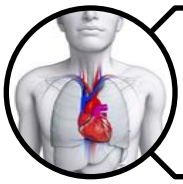
- Support respiration. Since they cause bronchospasm, First and most important step -before introducing any drug to the patient- is to control the patient's airway and provide him with adequate oxygen by artificial respiration.
- Atropine (to block muscarinic actions & CNS effects). Atropine has apposing effects of cholinomimetics.
- Cholinesterase reactivators **(Oximes e.g.: pralidoxime (PAM))**
  - First choice & most effective drugs.
  - Acts by regeneration (Re-Activation) of recently inhibited cholinesterase enzyme, if given before aging. By doing so, they reduce Ach effects.

Uses: I.V → over 15-30 min for organophosphate intoxication (poisoning).

Cholinomimetics (both direct and indirect)

Adverse effects:

Diarrhea



Bradycardia

Sweating & Salivation

Broncho-constriction

Contraindications:

Bronchial asthma

Peptic ulcer

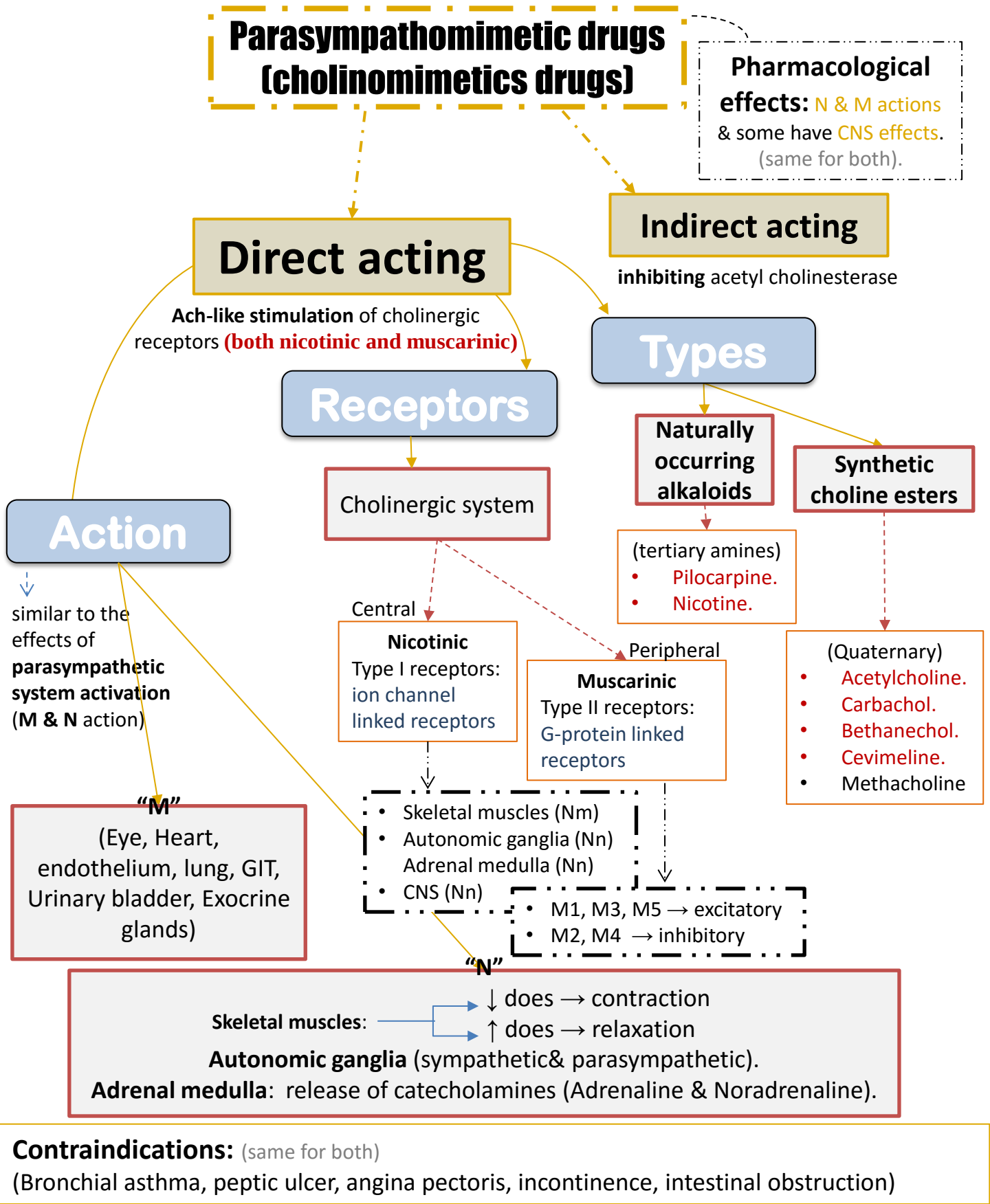
Urinary Incontinence

Angina pectoris

Intestinal obstruction

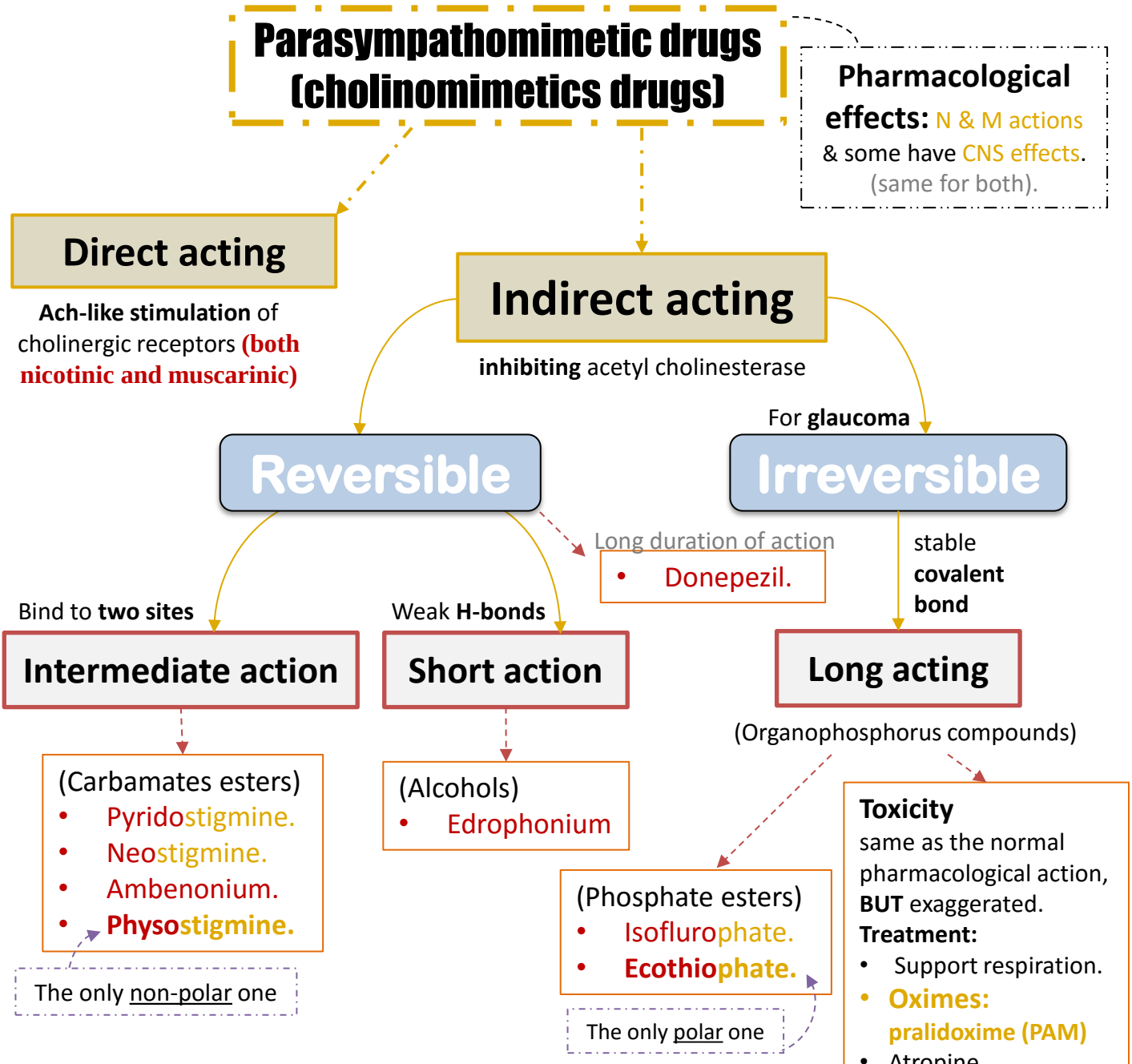
Disease	Drug/s for treatment	Type of cholinomimetics
Glaucoma (eye)	• **Pilocarpine** • **Carbachol**	direct
	• **Physostigmine** • **Ecothiophate**	indirect
Urinary retention and paralytic ileus	**Bethanechol**	direct
	Neostigmine	indirect
Myasthenia gravis	• **Pyridostigmine** • **Neostigmine** • **Ambenonium**	only indirect
Xerostomia (dryness of the mouth)	• **Pilocarpine** • **Cevimeline** (M3)	direct
Dementia of Alzheimer's disease	**Donepezil**	indirect

Mind map



Contraindications: (same for both)
(Bronchial asthma, peptic ulcer, angina pectoris, incontinence, intestinal obstruction)

Mind map



Characteristics of indirect acting drugs:

Mechanism: prevent hydrolysis of Ach by inhibiting acetyl cholinesterase.

Structure: similar in structure to Ach.

Adverse effects: (same for both direct and indirect cholinomimetics)
(Bradycardia, sweating & salivation, bronchoconstriction, diarrhea)

Contraindications: (same for both direct and indirect cholinomimetics)
(Bronchial asthma, peptic ulcer, angina pectoris, incontinence, intestinal obstruction)

Summery of Direct acting Drugs

	Synthetic choline esters (Quaternary ammonium compounds contain N+ (polar))				Naturally occurring alkaloids (tertiary amines)	
Drug	Acetylcholine	Carbachol	Bethanechol	Cevimeline	Pilocarpine	nicotine
Chemistry	Quaternary Polar	Quaternary Polar	Quaternary Polar	Quaternary Polar	Tertiary non polar	Tertiary non polar
Absorption	✗	better absorbed than Ach	better absorbed than Ach		Complete (well absorbed)	
Distribution	Poor	Poor	Poor	Poor	good distribution	
Metabolism by cholinesterase	✓	✗	✗		✗	
Duration	Very short	Longer (++)	Longer (++)		Longer (++)	
administration	• I.V. • eye drops	• Oral • eye drops • S.C.	• Oral • S.C.		• oral • eye drops	
Receptors	M, N	M, N	M	M3	M	
Selectivity	✗	Eye, GIT, Urinary bladder	GIT, Urinary bladder	Exocrine glands	More on eye, exocrine glands	
Uses	**Not used** cuz: • Not selective • Short action • rapid metabolism	Glaucoma	• **Paralytic ileus** • **Urinary retention**	• Sjogren's syndrome • Xerostomia	• **Glaucoma** • Xerostomia	causes alerting action (so does lobeline)
Adverse effects					• Profuse sweating • Salivation • Bronchoconstriction • Diarrhea • CNS effects	High level causes **convulsions & coma**
Excretion					Enhanced by acidification of urine	

Summery of Indirect acting Drugs

Reversible anticholinesterases

Drug	Actions	Kinetics	Pharmacokinetics	Uses
Alcohols (Short acting) (Weak **H-bonds**)				
Edrophonium	M, N	Very Short 5-15min polar	NOT absorbed orally, given by injection	• **Diagnosis of myasthenia gravis**
Carbamate esters (Intermediate acting) (Bind to **two sites**)				
Neostigmine Quaternary ammonium comp	M, N	Short 0.5-2hr polar	Can be used orally (polar) prominent on GIT & urinary tract.	• **Myasthenia gravis** treatment • Paralytic ileus • Urinary retention • Curare toxicity
Physostigmine Tertiary ammonium compound	M, N, CNS	Short 0.5-2hr non-polar	Good oral absorption	• **Glaucoma** (eye) • atropine toxicity
Pyridostigmine	M, N	Short 3-6 polar	-----	• **Myasthenia gravis** treatment
Ambenonium "not a stigmine derivative"	M, N	Short 4-8 polar	-----	• **Myasthenia gravis** treatment
Long acting				
Donepezil	M, N	Long	Given orally	• dementia of Alzheimer's disease

Irreversible anticholinesterases

Drug	Actions	Kinetics	Mechanism	Uses
Organophosphorus compounds (Long acting) (stable **covalent bond**)				
Isoflurophate	M, N, CNS	-----	-----	• dementia of Alzheimer's disease
Ecothiophate	M, N	Long 100hr, polar	Aging make bond extremely stable	• **Glaucoma**
pralidoxime (Oximes)	M, N, CNS	-----	reactivates recently inhibited enzymes before aging	• organophosphate intoxication

Study Questions

From Lippincott, for your own benefit.

Choose the ONE best answer.

4.1 Botulinum toxin blocks the release of acetylcholine from cholinergic nerve terminals. Which of the following is a possible effect of botulinum toxin?

A. Skeletal muscle paralysis.
B. Improvement of myasthenia gravis symptoms.
C. Increased salivation.
D. Reduced heart rate.

Correct answer = A. Acetylcholine released by cholinergic neurons acts on nicotinic receptors in the skeletal muscle cells to cause contraction. Therefore, blockade of ACh release causes skeletal muscle paralysis. Myasthenia gravis is an autoimmune disease where antibodies are produced against nicotinic receptors and inactivate nicotinic receptors. A reduction in ACh release therefore worsens (not improves) the symptoms of this condition. Reduction in ACh release by botulinum toxin causes reduction in secretions including saliva (not increase in salivation) causing dry mouth and an increase (not reduction) in heart rate due to reduced vagal activity.

4.2 A dentist would like to reduce salivation in a patient in preparation for an oral surgical procedure. Which of the following strategies will be useful in reducing salivation?

A. Activate nicotinic receptors in the salivary glands.
B. Block nicotinic receptors in the salivary glands.
C. Activate muscarinic receptors in the salivary glands.
D. Block muscarinic receptors in the salivary glands.

Correct answer = D. Salivary glands contain muscarinic receptors, not nicotinic receptors. Activation of muscarinic receptors in the salivary glands causes secretion of saliva. Blocking muscarinic receptors, using drugs such as atropine, reduces salivary secretions and makes the mouth dry.

4.3 Which of the following is a systemic effect of a muscarinic agonist?

A. Reduced heart rate (bradycardia).
B. Increased blood pressure.
C. Mydriasis (dilation of the pupil).
D. Reduced urinary frequency.
E. Constipation.

Correct answer = A. A muscarinic agonist binds to and activates muscarinic receptors in the heart, endothelial cells (blood vessels), the gut, and iris sphincter (eye) and urinary bladder wall muscles, in addition to several other tissues. Activation of muscarinic receptors by an agonist causes a reduction in heart rate, constriction of circular muscles in the iris sphincter leading to constriction of the pupil (miosis), increased GI motility (hence, diarrhea, not constipation), and contraction of bladder muscles leading to an increase (not decrease) in urination frequency. In the endothelial cells of blood vessels, muscarinic activation produces release of nitric oxide that causes vasorelaxation and a reduction (not increase) in blood pressure.

4.4 If an ophthalmologist wants to dilate the pupils for an eye examination, which of the following drugs/classes of drugs could be theoretically useful?

A. Muscarinic receptor activator (agonist).
B. Muscarinic receptor inhibitor (antagonist).
C. Acetylcholine.
D. Pilocarpine.
E. Neostigmine.

Correct answer = B. Muscarinic agonists (for example, ACh, pilocarpine) contract the circular smooth muscles in the iris sphincter and constrict the pupil (miosis). Anticholinesterases (for example, neostigmine, physostigmine) also cause miosis by increasing the level of ACh. Muscarinic antagonists, on the other hand, relax the circular smooth muscles in the iris sphincter and cause dilation of the pupil (mydriasis).

4.5 In Alzheimer's disease, there is a deficiency of cholinergic neuronal function in the brain. Theoretically, which of the following strategies will be useful in treating the symptoms of Alzheimer's disease?

A. Inhibiting cholinergic receptors in the brain.
B. Inhibiting the release of acetylcholine in the brain.
C. Inhibiting the acetylcholinesterase enzyme in the brain.
D. Activating the acetylcholinesterase enzyme in the brain.

Correct answer = C. Since there is already a deficiency in brain cholinergic function in Alzheimer's disease, inhibiting cholinergic receptors or inhibiting the release of ACh will worsen the condition. Activating the acetylcholinesterase enzyme will increase the degradation of ACh, which will again worsen the condition. However, inhibiting the acetylcholinesterase enzyme will help to increase the levels of ACh in the brain and thereby help to relieve the symptoms of Alzheimer's disease.

4.6 An elderly female who lives in a farm house was brought to the emergency room in serious condition after ingesting a liquid from an unlabeled bottle found near her bed, apparently in a suicide attempt. She presented with diarrhea, frequent urination, convulsions, breathing difficulties, constricted pupils (miosis), and excessive salivation. Which of the following is correct regarding this patient?

A. She most likely consumed an organophosphate pesticide.
B. The symptoms are consistent with sympathetic activation.
C. Her symptoms can be treated using an anticholinesterase agent.
D. Her symptoms can be treated using a cholinergic agonist.

Correct answer = A. The symptoms are consistent with that of cholinergic crisis. Since the elderly female lives on a farm and since the symptoms are consistent with that of cholinergic crisis (usually caused by cholinesterase inhibitors), it may be assumed that she has consumed an organophosphate pesticide (irreversible cholinesterase inhibitor). Assuming that the symptoms are caused by organophosphate poisoning, administering an anticholinesterase agent or a cholinergic agonist will worsen the condition. The symptoms are not consistent with that of sympathetic activation, as sympathetic activation will cause symptoms opposite to that of cholinergic crisis seen in this patient.

4.7 Sarin is a volatile nerve agent that inhibits cholinesterase enzymes. Which of the following symptoms would you expect to see in a patient exposed to sarin?

A. Urinary retention.
B. Tachycardia.
C. Constriction of pupils (miosis).
D. Dilation of the pupils (mydriasis).
E. Dry mouth.

Correct answer = C. Sarin is an organophosphate nerve gas that inhibits cholinesterase enzymes and increases ACh levels. Therefore, symptoms of cholinergic crisis (increased urination, bradycardia, excessive secretions, constriction of pupils, etc.) should be expected in patients exposed to sarin. Urinary retention, tachycardia, mydriasis, and dry mouth are usually seen with muscarinic antagonists.

4.8 Head and neck irradiation in cancer patients can decrease salivary secretion and cause dry mouth. All of the following drugs or classes of drugs are theoretically useful in improving secretion of saliva in these patients *except*:

A. Muscarinic antagonists.
B. Muscarinic agonists.
C. Anticholinesterase agents.
D. Pilocarpine.
E. Neostigmine.

Correct answer = A. Activation of muscarinic receptors in the salivary glands causes secretion of saliva. This can be achieved in theory by using a muscarinic agonist such as pilocarpine or an anticholinesterase agent such as neostigmine (increases levels of ACh). Muscarinic antagonists (anticholinergic drugs) will reduce salivary secretion and worsen dry mouth.

4.9 Which of the following drugs or classes of drugs will be useful in treating the symptoms of myasthenia gravis?

A. Nicotinic antagonists.
B. Muscarinic agonists.
C. Muscarinic antagonists.
D. Anticholinesterase agents.

Correct answer = D. The function of nicotinic receptors in skeletal muscles is diminished in myasthenia gravis due to the development of antibodies to nicotinic receptors in the patient's body (autoimmune disease). Any drug that can increase the levels of ACh in the neuromuscular junction can improve symptoms in myasthenia gravis. Thus, cholinesterase inhibitors help to improve the symptoms of myasthenia gravis. Muscarinic drugs have no role in myasthenia gravis, and nicotinic antagonists will worsen the symptoms.

4.10 *Atropa belladonna* is a plant that contains atropine (a muscarinic antagonist). Which of the following drugs or classes of drugs will be useful in treating poisoning with belladonna?

A. Malathion.
B. Physostigmine.
C. Muscarinic antagonists.
D. Nicotinic antagonists.

Correct answer = B. Atropine is a competitive muscarinic receptor antagonist that causes anticholinergic effects. Muscarinic agonists or any other drugs that can increase the levels of ACh will be able to counteract the effects of atropine. Thus, anticholinesterases such as malathion and physostigmine can counteract the effects of atropine in theory. However, malathion being an irreversible inhibitor of acetylcholinesterase is not used for systemic treatment in patients. Muscarinic antagonists will worsen the toxicity of atropine. Nicotinic antagonists could worsen the toxicity by acting on parasympathetic ganglionic receptors and thus reducing the release of ACh.

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

Lecture 3:

QUIZ1

QUIZ2

Lecture 4:

QUIZ

لولوه الصغير
شادن العمران
سارا الحسين
رغد المنصور
منيرة العمري
لمى الزامل
شهد البشر
كوثر الموسى

آية غانم
نوره البصيص
أمل العمران
اسرار باطرفي
نوف التويجري
ريما بن تويم
ديمه الراجحي
لينا الشهري

عبدالرحمن السياري
خالد الزهراني
عبدالله الجنيدل
أحمد المصعبي
مهند الزيد
عبدالرحمن الشمري
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