Drugs Affecting the Autonomic Nervous System-2
Cholinergic agents

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia

Cholinergic agents, Cholinomimetic drugs, parasympathomimetic drugs

Cholinergic agonists (parasympathomimetics):
Are drugs that mimic the effects of acetylcholine & promote the function of the neurotransmitter Ach either by binding to cholinocepors directly or mimic the effects of acetylcholine indirectly

Cholinergic drugs classified into

- Direct acting: which include:
  - Choline ester: Ach, Bethanechol, Carbachol.
  - Alkaloid: Pilocarpine, Muscarine, Nicotine.

- Indirect acting cholinergic agents which include:
  - Reversible: which divided into
    1. Short acting: edrophonium.
    2. Intermediate & long acting: neostigmine, physostigmine, pyridostigmine, tacrine.
  - Irreversible (very long acting):
    The organophosphorous e.g. echothiophate.
    Isoflurophate.

Table: Effects of direct-acting cholinoceptor stimulants.

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries	Dilation (via EDRF). Constriction (high-dose direct effect)
Veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

Direct acting cholinergic

Mimic the effects of acetylcholine by binding directly to cholinoceptors

Choline ester:

Acetylcholine :

- Quaternary ammonium compound
- Has both M & N activity.
- Acetylcholine as a drug is therapeutically of no importance because of:
  1. Multiplicity of action.
  2. Rapid inactivation by Acetylcholine esterase enzyme.

Mechanism of cholinergic drugs:

It has a mimic action of Ach, it binds with receptors on cell membrane of the target organ, changes the permeability of the cell membrane & permitting Ca and Na to flow into the cells, this depolarization in the cell membrane causing response

Choline ester:

Bethanechol

- It is structurally related to acetylcholine; the acetate is replaced by carbamate and the choline is methylated.
- It is not hydrolyzed by acetylcholinesterase (due to the addition of carbonic acid), although it is inactivated through hydrolysis by other esterases.
- It lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity.
- Its major actions are on the smooth musculature of the bladder and gastrointestinal tract. It has a duration of action of about 1 hour.

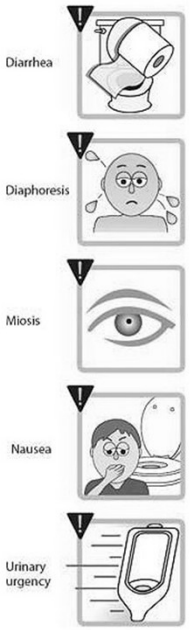
- Bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, non obstructive urinary retention.
- Bethanechol may also be used to treat neurogenic atony as well as megacolon.

Adverse effects of Bethanechol

Causes the effects of generalized cholinergic stimulation these include :

- Sweating
- Salivation
- Flushing
- Decreased blood pressure
- Nausea, abdominal pain, diarrhea
- Bronchospasm.

Some adverse effects observed with cholinergic drugs



Carbachol

- Carbachol is an ester of carbamic acid and a poor substrate for acetylcholinesterase
- It is biotransformed by other esterases, but at a much slower rate.
- It has both muscarinic as well as nicotinic actions.
- A single administration can last as long as 1 hour

- Carbachol is rarely used therapeutically because of
  - Its high potency
  - Receptor non selectivity
  - Relatively long duration of action
- Carbachol is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure

Alkaloid:

Muscarine

- It is of no therapeutic use. It is present in small amount in the fungus Amanita muscaria.

Nicotine:

- It is available as either gum or as patches used as an adjunct (aid) to stop tobacco smoking.

The alkaloid pilocarpine

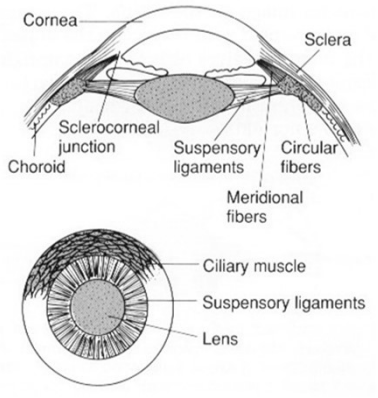
- Is a tertiary amine
- Is stable to hydrolysis by acetylcholinesterase compared with acetylcholine and its derivatives,
- Less potent than acetylcholine
- Will penetrate the CNS at therapeutic doses.
- Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

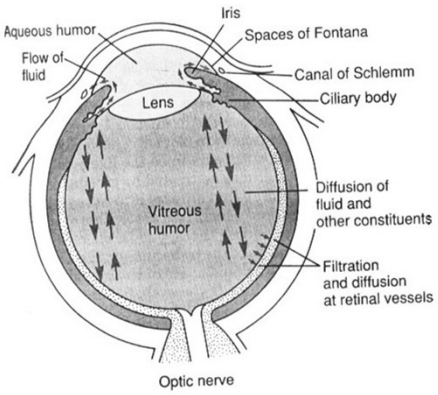
Effect of pilocarpine on the eye:

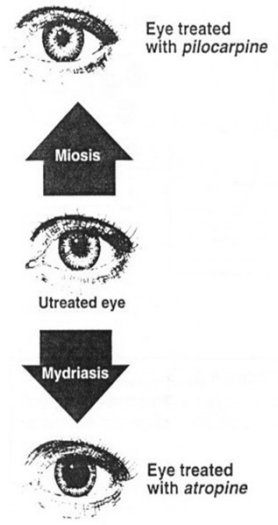
- Pupillary constriction (Miosis)
- Accommodation for near vision by contraction of the cilliary body and consequent increasing curvature of the lens.
- The intra ocular pressure falls as a result of miosis

Adverse effects of Pilocarpine

- Pilocarpine can enter the brain and cause CNS disturbances.
- It stimulates sweating and salivation.







Actions of *pilocarpine* and *atropine* on the iris and ciliary muscle of the eye.

- Pilocarpine used in both narrow-angle (closed-angle) and wide-angle glaucoma (open-angle)
- Pilocarpine available as tablet used for treatment of xerostomia (dry mouth), like that occur after irradiation of head & neck& also used in sjogren's syndrome.
- The intra ocular pressure falls as a result of miosis the (the iris is pulled away from the angle of anterior chamber & trabecular mesh work at base of cilliary muscle open so facilitate outflow of aqueous humor into canal of schlem which drain anterior chamber of eye).
- This action lasts up to 8 hours and can be repeated.

Note: Carbonic anhydrase inhibitors, such as acetazolamide, as well as the - β adrenergic blocker timolol, are effective in treating glaucoma chronically but are not used for emergency lowering of intraocular pressure.

Indirect acting cholinergic agents
Cholinesterase inhibitor or
Anticholinesterase

- Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Reversible)
- Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Irreversible)

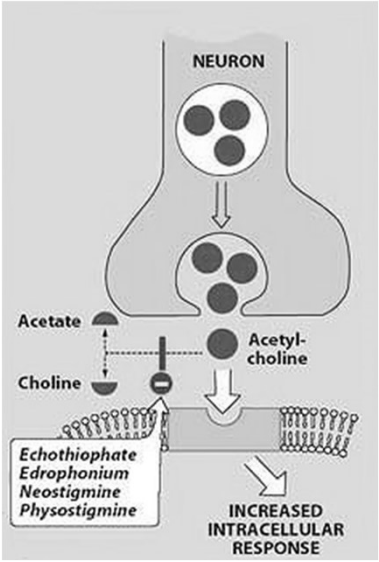
Indirect-Acting Cholinergic Agonsists:

Anticholinesterases (Reversible)

- Inhibitors of acetylcholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings.
- This results in the accumulation of acetylcholine in the synaptic space
- These drugs can thus provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the autonomic nervous system, as well as at neuromuscular junctions and in the brain.

Note: Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions. It is located both pre- and post synaptically in the nerve terminal

Mechanisms of action of indirect (reversible) cholinergic agonists



Indirect acting Cholinesterase inhibitor, Reversible

1. Short acting

Edrophonium:

- Is a quaternary amine
- It is more rapidly absorbed
- Has a short duration of action of 10 to 20 minutes
- Is used in the diagnosis of myasthenia gravis, Intravenous injection of edrophonium leads to a rapid increase in muscle strength.
- Care must be taken, because excess drug may provoke a cholinergic crisis. Atropine is the antidote

2. Intermediate & long acting

Physostigmine

- Effects, not only the muscarinic and nicotinic sites of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction are stimulated.
- Its duration of action is about 2 to 4 hours.
- Physostigmine can enter and stimulate the cholinergic sites in the CNS.

Therapeutic uses of Physostigmine

- The drug increases intestinal and bladder motility (used in atony of either organ)
- It is used to treat glaucoma, but pilocarpine is more effective (topically in the eye, it produces miosis and spasm of accommodation, as well as a lowering of intraocular pressure).
- Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, phenothiazines, and tricyclic antidepressants.

Adverse effects:

- Convulsions (high doses)
- Bradycardia and a fall in cardiac output
- Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of acetylcholine and, ultimately, results in paralysis of skeletal muscle. (Rarely seen with therapeutic doses).

Neostigmine

- Moderate duration of action, usually 30 minutes to 2 hours
- More polar than physostigmine and not enter the CNS(not used to overcome toxicity of central-acting antimuscarinic agents such as atropine)
- Its effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes.

- It is used to stimulate the bladder and GI tract
- It is also used as an antidote for tubocurarine and other competitive neuromuscular blocking agents
- Neostigmine has found use in symptomatic treatment of myasthenia gravis (an autoimmune disease caused by antibodies to the nicotinic receptor at neuromuscular junctions. This causes their degradation and, thus, makes fewer receptors available for interaction with the neurotransmitter)

Adverse effects of neostigmine

- Salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

Pyridostigmine

- Is cholinesterase inhibitor that is used in the chronic management of myasthenia gravis.
- Durations of action is intermediate (3 to 6 hours) but longer than that of neostigmine.
- Used orally & paranterally
- Adverse effects of this agent is similar to those of neostigmine

Cholinesterase inhibitors neostigmine or pyridostigmine) are the drugs of choice, they are given intravenously or intramuscularly to reverse the pharmacologic muscle paralysis which occurs in surgical anesthesia due to use nondepolarizing neuromuscular blocking drugs (muscle relaxants) such as tubocurarine.

Indirect acting Cholinesterase inhibitor,
Irreversible (Very long acting)

Echothiophate

- An ophthalmic solution of the drug is used directly in the eye for the chronic treatment of open-angle glaucoma (not a first-line agent).
- The effects may last for up to one week after a single administration.
- In addition to its other side effects, the potential risk for causing cataracts limits the use of echothiophate.

Indirect-Acting Cholinergic Agonsists:

Anticholinesterases (Irreversible)

- A number of synthetic organophosphate compounds have the capacity to bind covalently to acetylcholinesterase.
- The result is a long-lasting increase in acetylcholine at all sites where it is released.

- Used in agriculture or pesticides & insecticides
- Many of these drugs are extremely toxic and were developed by the military as nerve agents
- GA (Tabun); GB (Sarin) and GD (Soman) called Nerve gases, although they are volatile liquids

Poisoning with cholinesterase inhibitors (Organophosphorous poisoning)

- An organophosphate that covalently binds to acetylcholinesterase
- The enzyme is permanently inactivated
- Recovery is usually within days.

Treatment of Organophosphorous poisoning:

1. Removal of the clothes, washing of the skin .
2. Atropine (antimuscarinic drug) parenterally in large doses (atropine dose is l-2mg I.V. every 15-60 min, until sings of effect appear:
   (dry mouth & heart rate in excess of' 70 beats/min).

3. Mechanical ventilation to assist respiratory muscle(Because atropine has antimuscarinic effect only)
4. Treatment convulsions (by Diazepam)
5. Atropine eye drops(to relieve headache caused by meiosis)
6. Pralidoxime this can reactivate the inhibited acetylcholinesterase and regenerates this enzyme.

Note: prophylaxis by pyridostigmine, which occupies cholinesterase reversibly for few hours(if there is risk of exposure)