DIRECT-ACTING CHOLINERGIC AGONISTS

- **Acetylcholine**
- **Bethanechol**
- **Carbachol (carbamylcholine)**
- **Pilocarpine**

Acetylcholine

- ✓Quaternary ammonium compound that cannot penetrate membranes.

- ✓ACh has both muscarinic and nicotinic activity

Acetylcholine

- Its effects include :

➢ **Decrease in heart rate and cardiac output**

➢ **Decrease in blood pressure :**ACh activates M3 receptors found on endothelial cells lining

the smooth muscles of blood vessels. This results in the production of nitric oxide

Other effects:

- Diarrhea
- Diaphoresis
- Nausea
- Miosis
- Bronchospasm
- Incease in salivation and GIT motility, Increase urinary urgency

Bethanechol

- Not hydrolyzed by AChE *(due to the esterification of carbamic acid)*
- Inactivated through hydrolysis by other esterases.
- It lacks nicotinic actions *(due to the addition of the methyl group)*
- Have strong muscarinic activity.
- Its major actions are on the smooth musculature of the bladder and GI tract.
- It has about a 1-hour duration of action.

- used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. *Bethanechol may* also be used to treat neurogenic atony .

Adverse effects:

- ❖salivation
- ❖flushing,
- ❖decreased blood pressure,
- ❖nausea, abdominal pain, diarrhea,
- ❖bronchospasm.

Carbachol (carbamylcholine)

- causes the effects of generalized cholinergic stimulation (non selective, long acting)
- *Carbachol has profound effects on both the cardiovascular* and GI systems, also causes miosis in the pupil
- It can cause release of epinephrine from the adrenal medulla by its nicotinic action.

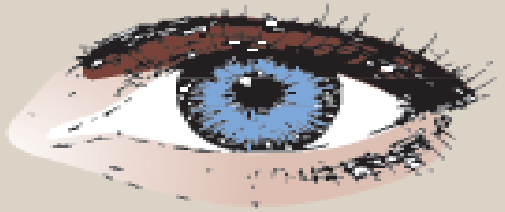
- ✓*carbachol is rarely used* therapeutically except in *the eye as a miotic agent* to treat glaucoma

  by causing pupillary contraction and a decrease in intraocular pressure.

The topical use of carbacol limits its systemic side effects

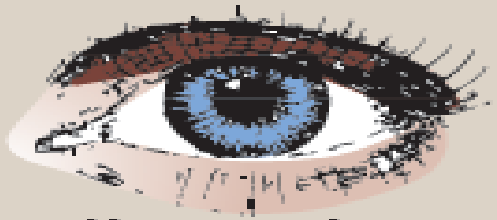
Pilocarpine

- An alkaloid
- Mainly used in ophthalmology
- Has a muscarinic activity
- *pilocarpine produces rapid* miosis and contraction of the ciliary muscle.
- Pilocarpine is one of the most effective secretagoges of saliva and sweat and tears when given systimically



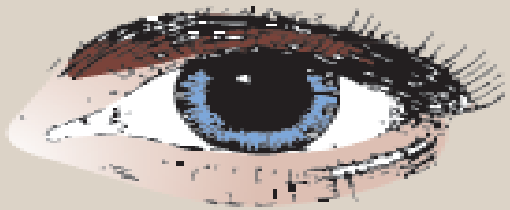
Eye treated with *pilocarpine*

Miosis
(contraction of the pupil)



Untreated eye

Mydriasis
(dilation of the pupil)



Eye treated with *atropine*

Therapeutic use in glaucoma :

➢ *Pilocarpine is used to treat glaucoma*

and is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma.

- Check also Acetazolamide, timolol for glucoma

❖ Adverse effects :

- Diaphoresis, salivation, CNS disorders

ATROPINE is the recommended Antidot.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ACETYLCHOLINESTERASE INHIBITORS (REVERSIBLE)

- AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions.
- It is located both pre- and postsynaptically

✓ *Inhibitors of AChE indirectly provide a cholinergic action by prolonging the lifetime of ACh produced endogenously at the cholinergic nerve endings*.

✓ This results in the accumulation of ACh in the synaptic space

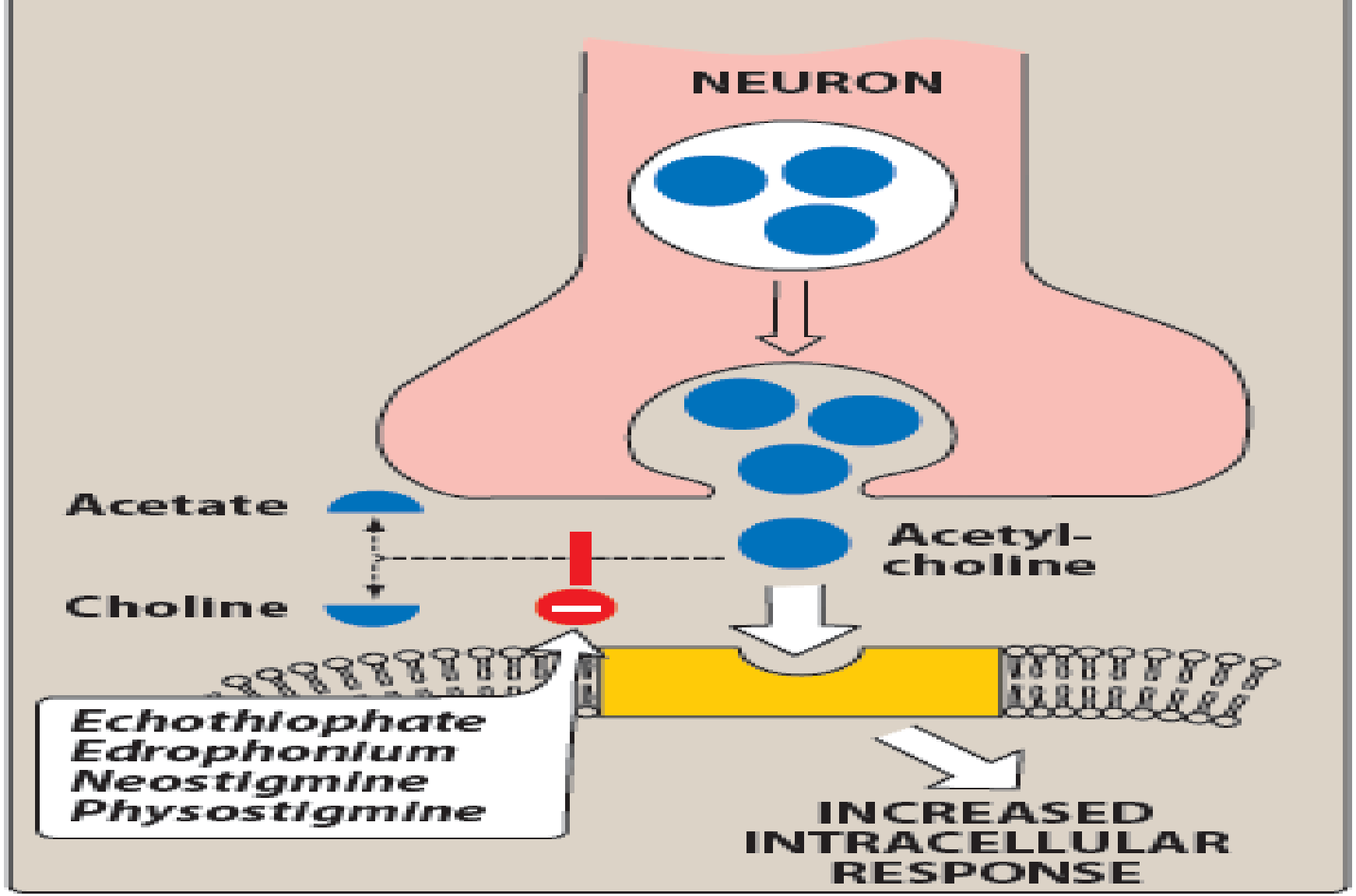


Figure 4.8
Mechanisms of action of indirect (reversible) cholinergic agonists.

- ACHE Inhibitors posses activity at All cholinergic receptors including:

➢ Nicotinic Receptors

➢ Muscarinic Receptors

➢ NMJ (neuromuscular junction receptors)

- The reversible AChE inhibitors can be broadly classified as:

1. short-acting agents

2.intermediate-acting agents

ACHE Inhibitors

- **Edrophonium**
- **Physostigmine**
- **Neostigmine**
- **Pyridostigmine and ambenonium**
- **Tacrine, donepezil, rivastigmine, and galantamine**

Edrophonium

✓The prototype short-acting AChE inhibitor.

✓ Reversibly inhibits ACHE

✓ Quaternaty ammonium , short acting

✓ No CNS penetration

✓Limited use clinically

Physostigmine

- ✓ Found in plants, a tertiary amine
- ✓ stimulates muscarinic and nicotinic sites of

the ANS and nicotinic receptors of the NMJ.

- ✓ Its duration of action is about 2 to 4 hours, (intermediate- acting agent)
- ✓ Used to stimulate intestinal and blader motility in cases of atony
- ✓ used to treat glaucoma, but *pilocarpine is more effective*

Adverse effects

- Physostigmine causes:

❖ Convulsions

❖Bradycardia

❖ Muscle paralysis (rarely seen at therapeutic doses)

❖Hypotension

Neostigmine

- synthetic compound similar to physostigmine
- quaternary ammonium , polar, (intermidaite acting)
- More effective on muscular tissues compared to physostigmine
- Therapeutic uses: It is used to stimulate the bladder and GI tract

Adverse Effects :

- ❖ Generalized cholinergic stimulation, such as
  - salivation
  - nausea
  - flushing
  - Abdominal pain
  - decreased blood pressure
  - diarrhea
  - bronchospasm.
- ❖ Neostigmine lacks CNS related side effect.
- ❖ Contraindicated in intestinal or urinary bladder obstruction

- **Pyridostigmine and ambenonium**

➢ *Pyridostigmine and ambenonium* are other cholinesterase inhibitors that are used in the chronic management of myasthenia gravis. Their durations of action are intermediate

(3 to 6 hours and 4 to 8 hours, respectively), but longer than that of *neostigmine.*

➢ *Adverse eff ects of these agents are similar to those* of *neostigmine.*

Tacrine, donepezil, rivastigmine, and galantamine

- Used in AD
- GI distress is the major side effect

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASES (IRREVERSIBLE)

Echothiophate

- Organophosphate insecticide
- Irreversible inhibitor of ACHE
- Effect lasts for 1 week
- Generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions.
- *Echothiophate produces intense miosis and, thus, has* found therapeutic use

Reactivation of acetylcholinesterase

- *Pralidoxime*
- *Atropine*
- *Diazepam*

Bethanechol

- Used in treatment of urinary retention
- Binds preferentially at muscarinic receptors

Physostigmine

- Increases intestinal and bladder motility
- Reduces intraocular pressure in glaucoma
- Reverses CNS and cardiac effects of tricyclic antidepressants
- Reverses CNS effects of *atropine*
- Uncharged, tertiary amine that can penetrate the CNS

Rivastigmine, galantamine, donepezil

- Used as first-line treatments for Azheimer disease, though confers modest benefit
- Have not been shown to reduce healthcare costs or delay institutionalization
- Can be used with *memantine* (N-methyl-D-aspartate antagonist) with moderate to severe disease

Carbachol

- Produces miosis during ocular surgery
- Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*

Neostigmine

- Prevents postoperative abdominal distention and urinary retention
- Used in treatment of myasthenia gravis
- Used as an antidote for *tubocurarine*
- Has long duration of action (2 to 4 hrs)

Echothiophate

- Used in treatment of open-angle glaucoma
- Has long duration of action (1 week)

Pilocarpine

- Reduces intraocular pressure in open-angle and narrow-angle glaucoma
- Binds preferentially at muscarinic receptors
- Uncharged, tertiary amine that can penetrate the CNS

Edrophonium

- For diagnosis of myasthenia gravis
- As antidote for tubocurarine
- Has short duration of action (10 to 20 min)

Acetylcholine

- Has no therapeutic uses