

DIRECT-ACTING CHOLINERGIC AGONISTS

cholinergic agonist → activation of parasympathetic

- Acetylcholine

رج ینفردنا کل ال
preganglionic
عضلاتا
postganglionic
درج تاثر علی NMJ .

- Bethanechol

- Carbachol (carbamylcholine)

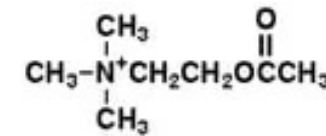
- Pilocarpine

بالتکلی هر رج يرتبط
* nicotinic
* muscarinic
* NMJ

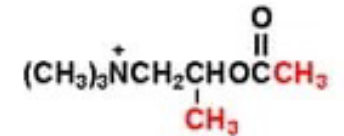
رج ترتبط علی receptors الی تحفز ال acetylcholine .
direct acting
cholinergic agonist
یعنی ترتبط علی muscarinic & nicotinic

indirect cholinergic agonist
رج تحفز ال acetylcholine یزید کیف؟؟ عن طریق
acetylcholinesterase أعطی دواء یشد .

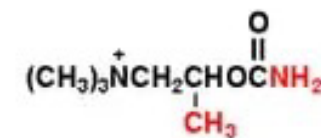
Structure of Acetylcholine and its Derivatives



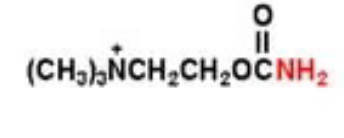
Acetylcholine



Methacholine



Bethanechol



Carbachol

ما في عذري دواء ACh

Acetylcholine

تغيزال
parasympathetic.

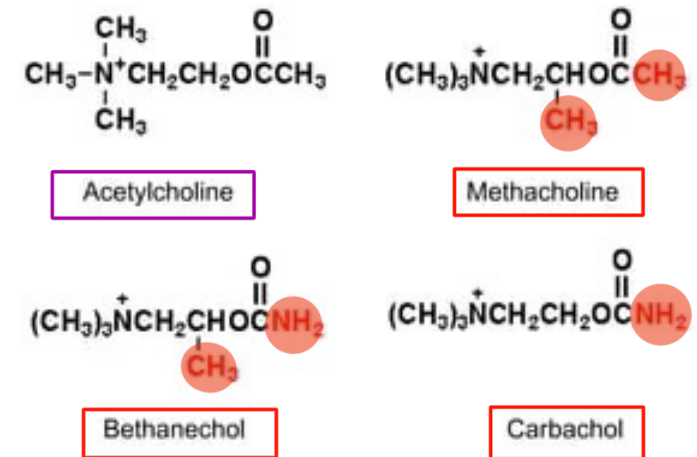
charged

- ✓ Quaternary ammonium compound that cannot penetrate membranes.

اينا ممكن اعشاش ابي مركب بيغل داخل الخلية لازم يكون
unionized (غير مشحون) و عا أتة ACh يغير charged معناها ما
تج يغل داخل الخلية cell membrane.

- ✓ ACh has both muscarinic and nicotinic activity

Structure of Acetylcholine and its Derivatives



Cholinergic agonist

Acetylcholine

تأثيره على الجسم لفترة قصيرة جداً لأنه عنيف enzyme ينشط ACh والي هو AChE .

- Its effects include :

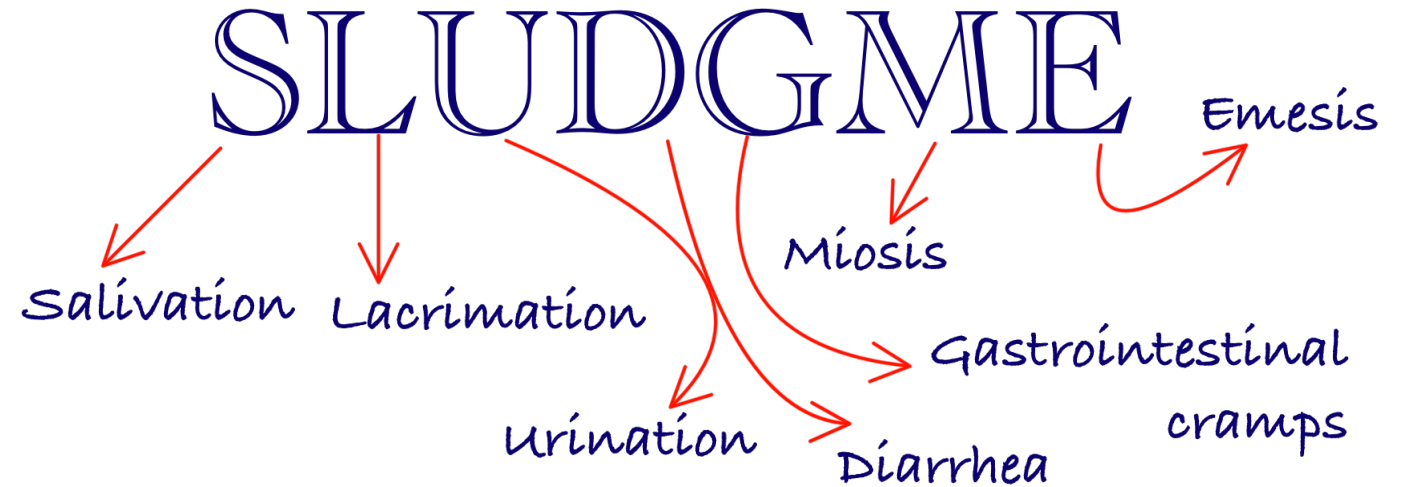
- Decrease in heart rate and cardiac output

- 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

vasodilation

Other effects:

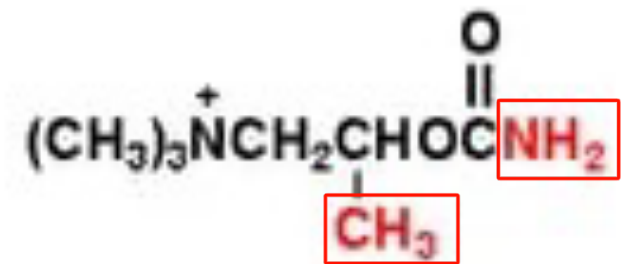
- Diarrhea
- Diaphoresis تعرق
- Nausea
- Miosis (pupil contraction)
- Bronchospasm تشنج القصبات
- Increase in salivation and GIT motility, Increase urinary urgency



الحاجة الملحة للتبول زرع مبادئ diuretics

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.
contraction (pointing to bladder)
urination (pointing to bladder)
increase GI motility (pointing to GI tract)
- It has about a 1-hour duration of action.



Bethanechol

ارتقاء / كسل جالطانية

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

احتباس البول

التبول العصبى / غير فى الاعصاب

Cholinergic agonist → bladder contraction

* هذا الدواء لا يستخدم لتحفيز urination
في حالات urinary obstruction.

جميع هذه الأدوية ممنوعة
مرض asthma.

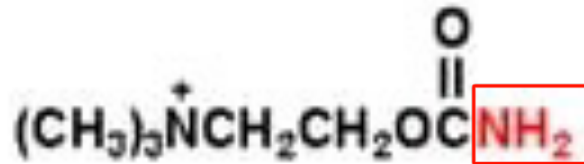
Adverse effects:

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

لا يستخدم systemic هو فقط
يستخدم topical

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

✓ *carbachol is rarely used therapeutically except in the*
eye as a miotic agent to treat glaucoma → increase intraocular pressure .
by causing pupillary contraction and a decrease in intraocular pressure.
relaxation of ciliary muscle .
contraction of ciliary muscle .

The topical use of carbacol limits its systemic side effects

Pilocarpine

من أهم الأدوية التي يتم استخدامها
to induce miosis.

side effect of topical drug
التي تكون أقل تحسناً أعطى systemically

- An alkaloid
- Mainly used in ophthalmology
- Has a muscarinic activity على عكس أدوية ال cholinergic antagonist mydriasis التي تقل e.g. atropine.
- *pilocarpine* produces rapid miosis and contraction of the ciliary muscle.
- Pilocarpine is one of the most effective secretagogues of saliva and sweat and tears when given systemically



Eye treated
with pilocarpine

→ cholinergic agonist



→ parasympathetic



Untreated eye



→ sympathetic



Eye treated
with atropine

→ anti-cholinergic
(cholinergic antagonist)

⊕ Therapeutic use in glaucoma :

➤ Pilocarpine is used to treat glaucoma

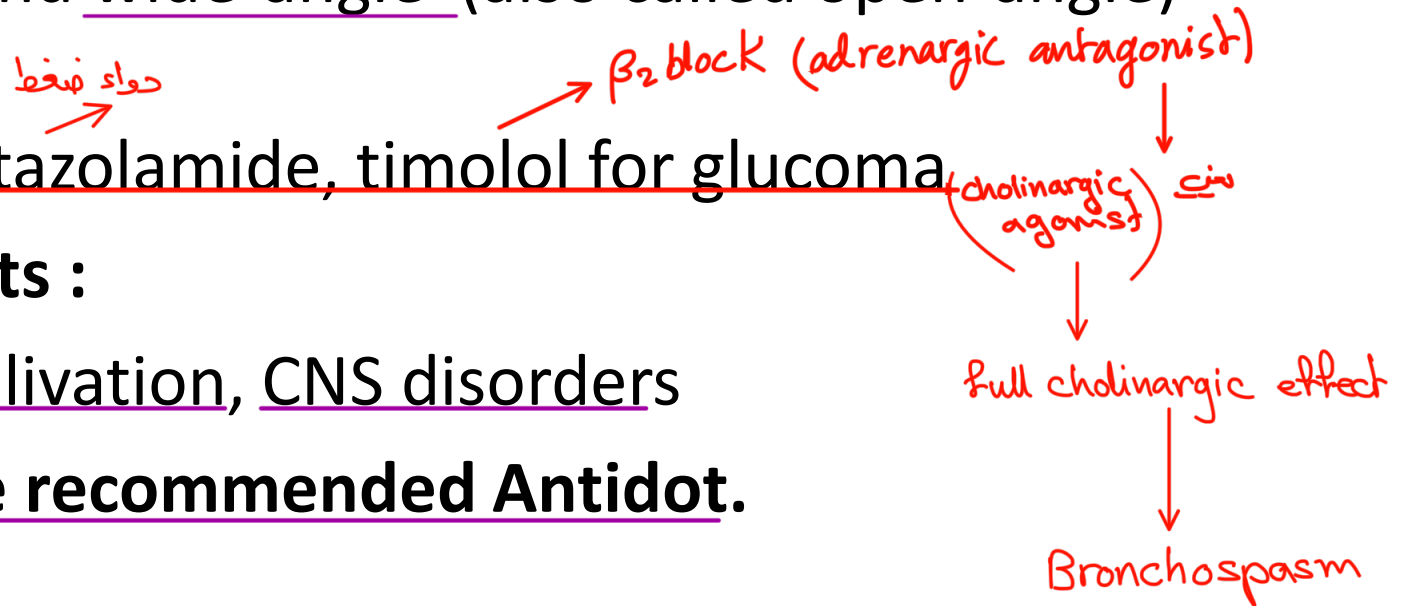
and is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma.

- Check also Acetazolamide, timolol for glaucoma

❖ Adverse effects :

- Diaphoresis, salivation, CNS disorders

ATROPINE is the recommended Antidot.



← نور

**INDIRECT-ACTING CHOLINERGIC
AGONISTS:
ACETYLCHOLINESTERASE
INHIBITORS (REVERSIBLE)**

← معني الارتباط مع يكون لفترة ويعودها
مع يترك AChE وبالتالي AChE مع يرجع لشيغل

- 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

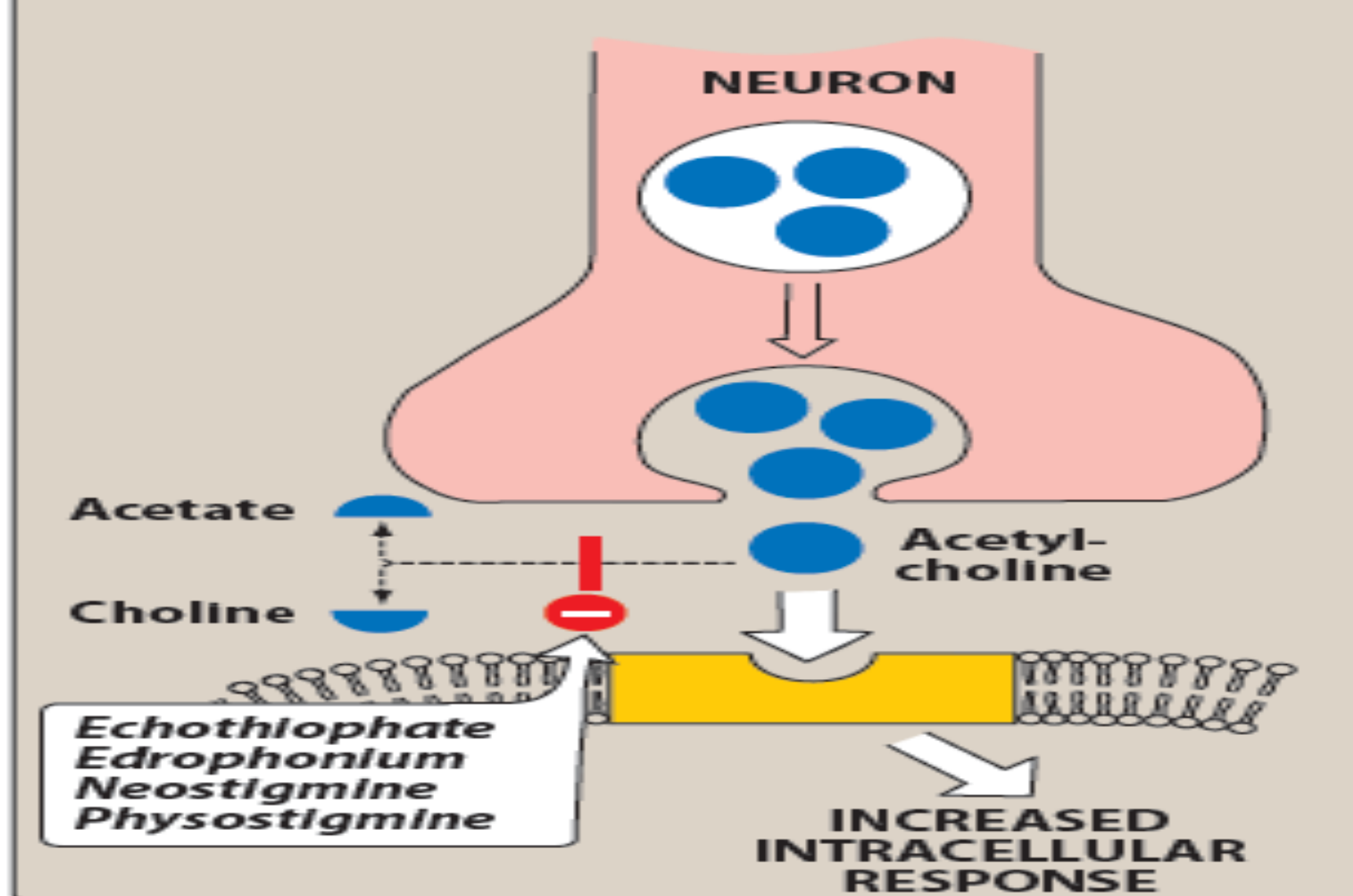


Figure 4.8
Mechanisms of action of indirect (reversible) cholinergic agonists.

- **ACHE Inhibitors** possess 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 for AD

Edrophonium

(النموذج الأول) ← يعني هو أول دواء تم اختراعه منتهي المجموعة (AChE) inhibitor.

✓ The prototype short-acting AChE inhibitor.

✓ Reversibly inhibits AChE

✓ Quaternary ammonium , short acting

✓ No CNS penetration

✓ Limited use clinically

لأنه لا يدخل داخل
cell membrane.

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 bladder motility in cases of atony
- ✓ used to treat glaucoma, *but pilocarpine is more effective*

Adverse effects

- **Physostigmine causes:**

← قسطنجات

- ❖ Convulsions (contraction of skeletal muscle)

- ❖ Bradycardia

- ❖ Muscle paralysis (rarely seen at therapeutic doses)

- ❖ Hypotension

↓
في حالة
reversible

• أهم عضلة إرادية عندنا بالجسم
• diaphragm
- لا نزا مرتبطة بعملية التنفس .

Neostigmine

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

charge

- No CNS
side effects .

Adverse Effects :

❖ Generalized cholinergic stimulation, such as

- salivation
- nausea
- flushing
- Abdominal pain
- decreased blood pressure
- diarrhea
- bronchospasm.

❖ Neostigmine lacks CNS related side effect.

موانع استخدام

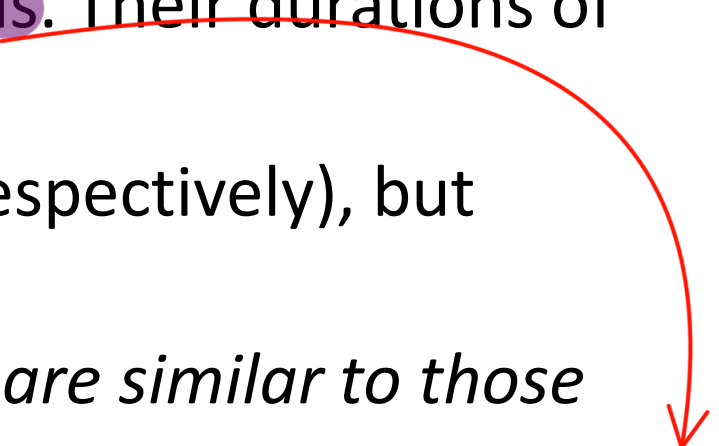
❖ Contraindicated in intestinal or urinary bladder obstruction

- **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 effects of these agents are similar to those of neostigmine.*



a chronic autoimmune disorder in which antibodies destroy the communication between nerves and muscle, resulting in weakness of the skeletal muscles.

Tacrine, donepezil, rivastigmine, and galantamine

- Used in AD → Alzheimer disease
- GI distress is the major side effect

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASES (IRREVERSIBLE)

→ long acting

← ارتباط دائم

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*

مبيد حشرات



يعني هاد الانزيم
رج يبطل يشتغل بالمره



Reactivation of acetylcholinesterase

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

Summary

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 <i>atropine</i> ● Uncharged, tertiary amine that can penetrate the CNS	Rivastigmine, galantamine, donepezil ● Used as first-line treatments for Alzheimer disease, though confers modest benefit ● Have not been shown to reduce healthcare costs or delay institutionalization ● Can be used with <i>memantine</i> (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 <i>pilocarpine</i>	Neostigmine ● Prevents postoperative abdominal distention and urinary retention ● Used in treatment of myasthenia gravis ● Used as an antidote for <i>tubocurarine</i> ● 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