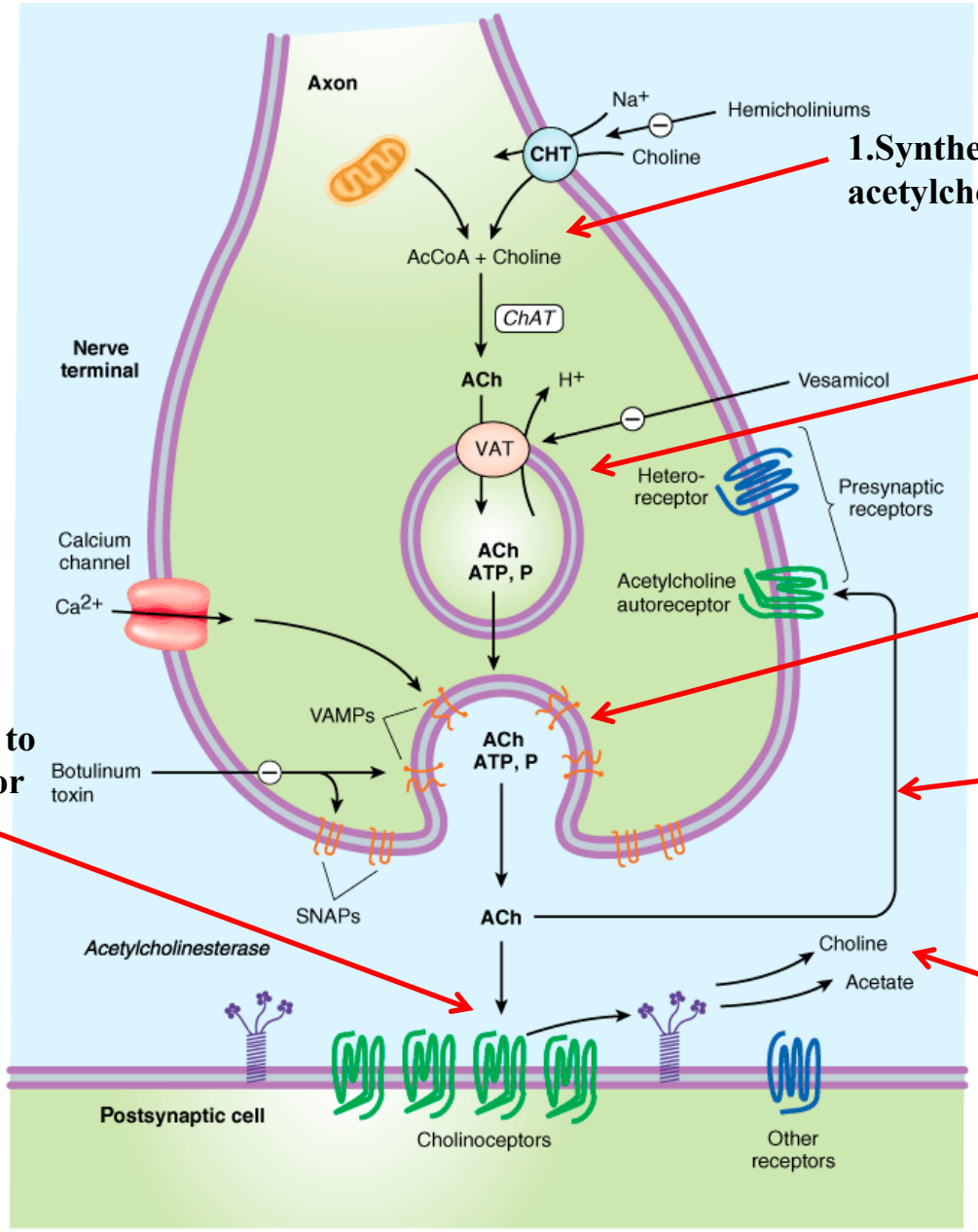
CHOLINOCEPTOR-ACTIVATING & CHOLINESTERASE-INHIBITING DRUGS



1.Synthesis of acetylcholine (Ach)

2.Storage of acetylcholine (Ach) in vesicles

3. Release of acetylcholine (Ach)

4. Binding to the receptor

6. Modulation of Ach release

5. Degradation of acetylcholine

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

OVERVIEW

- **Drugs affecting the ANS** are divided into two groups according to the type of neuron involved in the mechanism of action:
  a) The **cholinergic drugs**: they act on receptors that are activated by acetylcholine (Ach)
  b) The **adrenergic drugs**: they act on receptors that are activated by norepinephrine or epinephrine

- **Cholinergic and adrenergic drugs** both act by either **stimulating or blocking** receptors of the ANS

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

- **Cholinoceptor** denotes **receptors** that **respond** to **acetylcholine**

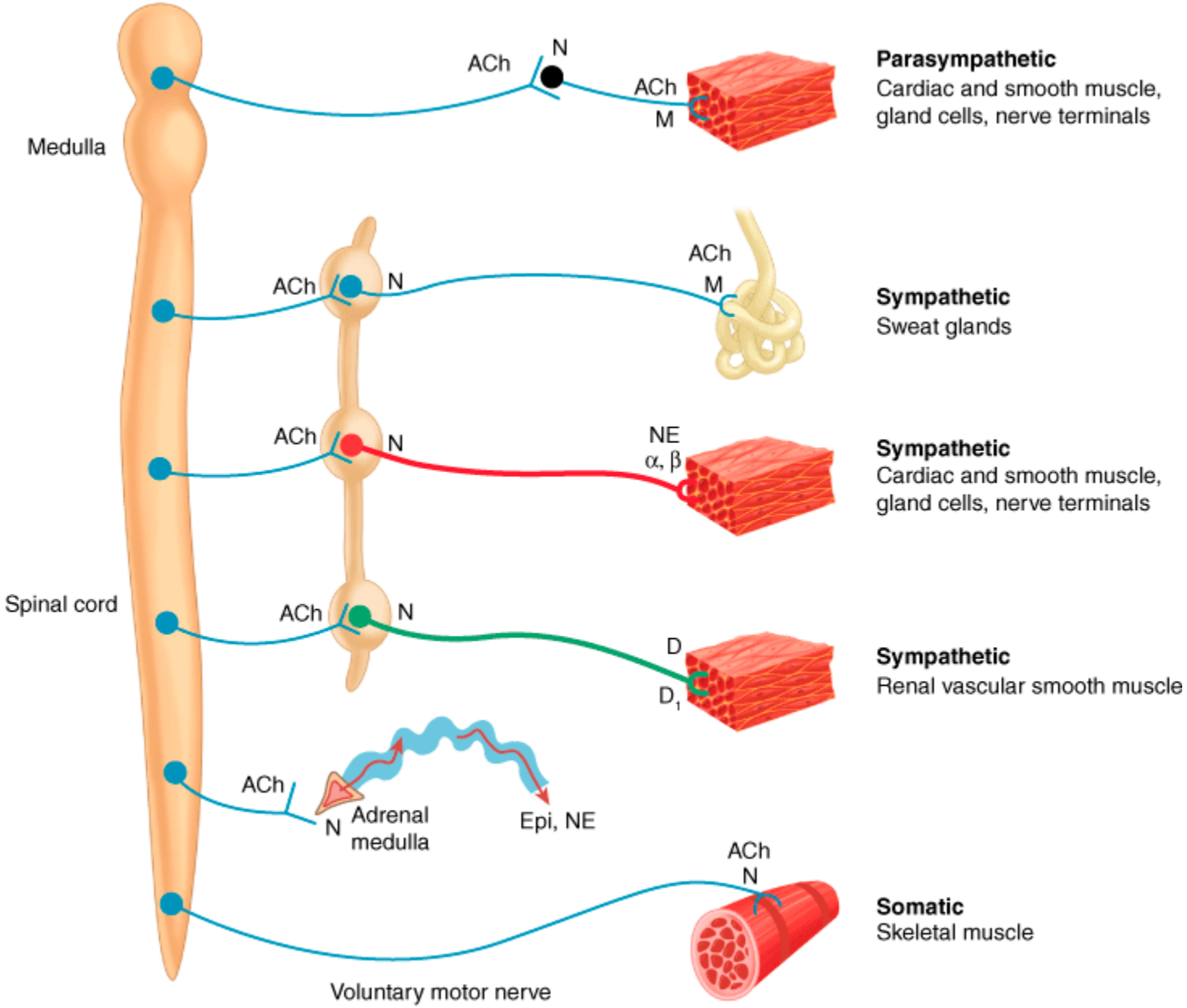
- **Two families/subtypes** of cholinoceptors were **named after the alkaloids** originally **used** in **their identification**:
  - nicotinic (N) and
  - muscarinic (M) receptors

I. NICOTINIC (*N*) RECEPTORS

- These receptors,
  - in addition to **binding ACh**,
  - **also recognize nicotine**,
  - but show a **week affinity** for **muscarine**

- **N receptors** are
  - **transmembrane polypeptide**
  - whose **subunits form cation-selective ion channels**

- N receptors are located on plasma membranes:
  - of postganglionic cells in all autonomic ganglia,
  - of muscles innervated by somatic motor fibers (i.e. **Neuromuscular junction**),
  - and of some CNS neurons



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

MECHANISM OF ACTION

- **Binding** of **2 Ach** molecules causes:
  - channel opening
  - with a **rapid influx of sodium and potassium ions** (calcium ions may also carry charge through the nicotinic receptor ion channel)

- This triggers depolarization of the cell and elicits:
  - a neruronal action potential (in postganglionic nerve)
  - or muscle contraction (in skeletal muscles)

- N receptors located at the neuromuscular junction are sometimes designated NM and the ganglionic (neuronal) receptors are designated NN

II. MUSCARINIC (*M*) RECEPTORS

- Activation of **M1, M3, and M5** receptors produces an:
  - **IP3, DAG (M1, M3)**and stimulation of **adenylyl cyclase**

- These receptors are primarily responsible for activating Ca^{+2}-dependent responses, such as
  - secretion by glands
  - and the contraction of smooth muscle

- Activation of *M2 and M4* receptors:
  - *inhibits adenylyl cyclase*

II. MUSCARINIC (*M*) RECEPTORS

- Muscarinic receptors: (GPCR)
  - Contains 7 transmembrane domains whose **third cytoplasmic** loop is **coupled to G** proteins
  - In general, **regulate** the **production of second messengers**
  - Five subclasses of muscarinic receptors: M_1, M_2, M_3, M_4, and M_5 have been identified

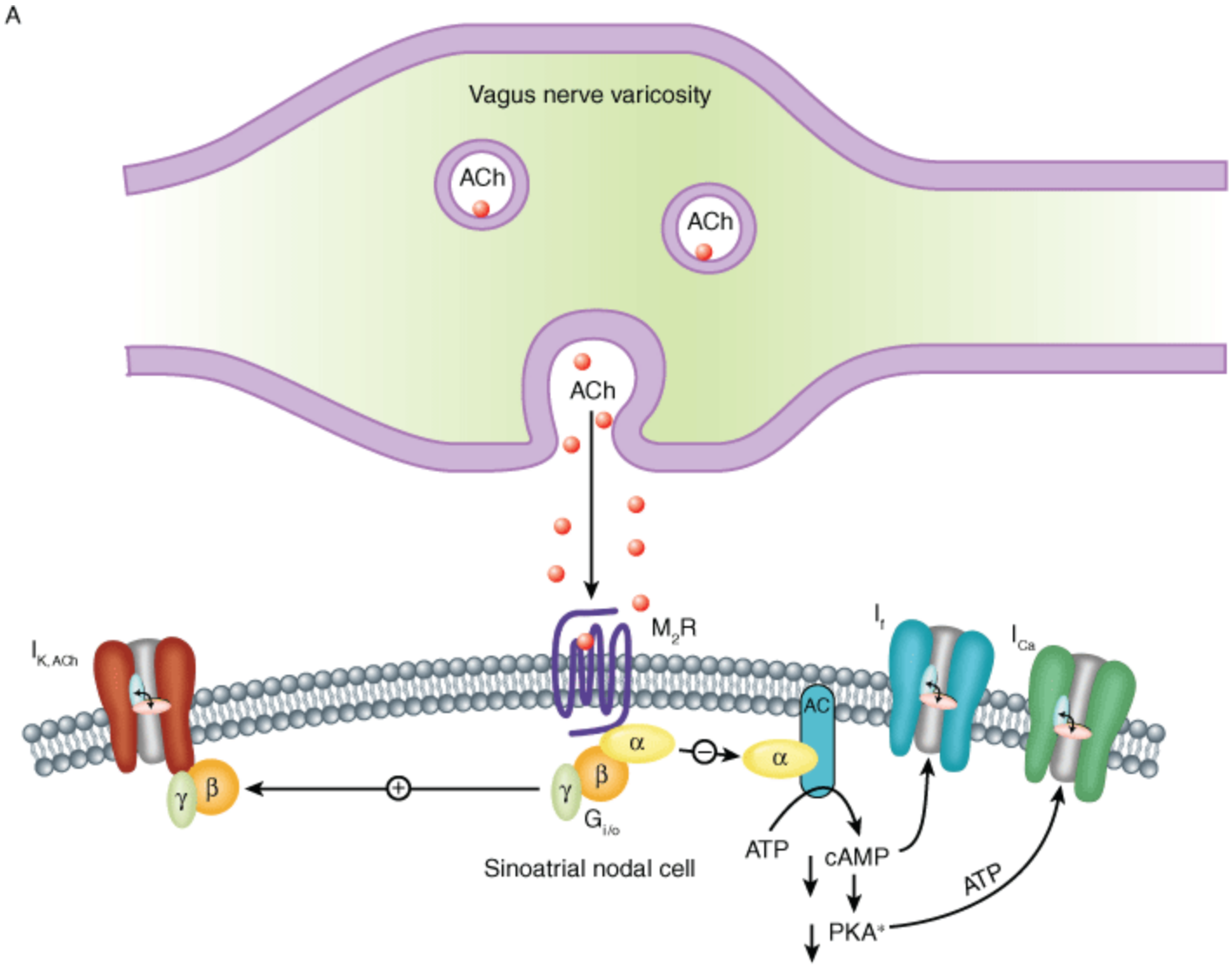
Subtypes and Characteristics of Cholinoceptors

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M_1	Neural	Nerves	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_2	Cardiac M_2	Heart, nerves, smooth muscle	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production, activation of K^+ channels!
M_3	Glandular	Glands, smooth muscle, endothelium!	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade, Increase cGMP!
M_4		CNS?	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production
M_5		CNS?	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
N_M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer $[(1)_2 1)]$	Na^+, K^+ depolarizing ion channel
N_N	Neuronal type, ganglion receptor	CNS postganglionic cell body, dendrites	Pentamer with 2 subunits only, eg, $(4)_2(2)_3$ (CNS) or 3 $5(2)_3$ (ganglia)	Na^+, K^+ depolarizing ion channel

MECHANISM OF ACTION

- **One** involves G_q-protein coupling of M_1 and M_3 receptors to the release of the second messengers, **diacylglycerol (DAG)** and **inositol-1,4,5-trisphosphate (IP_3)**
  - DAG modulates the action of protein kinase C, an enzyme important in secretion,
  - whereas IP_3 evokes the release of calcium from intracellular storage sites, which results in contraction in smooth muscle
- A **second** mechanism couples M_2 muscarinic receptors to adenylyl cyclase through the inhibitory G_i-coupling protein
- A **third** mechanism couples the same M_2 receptors via the subunit of the G protein to potassium channels in the heart and elsewhere
  - Muscarinic agonists facilitate opening of these channels

M2

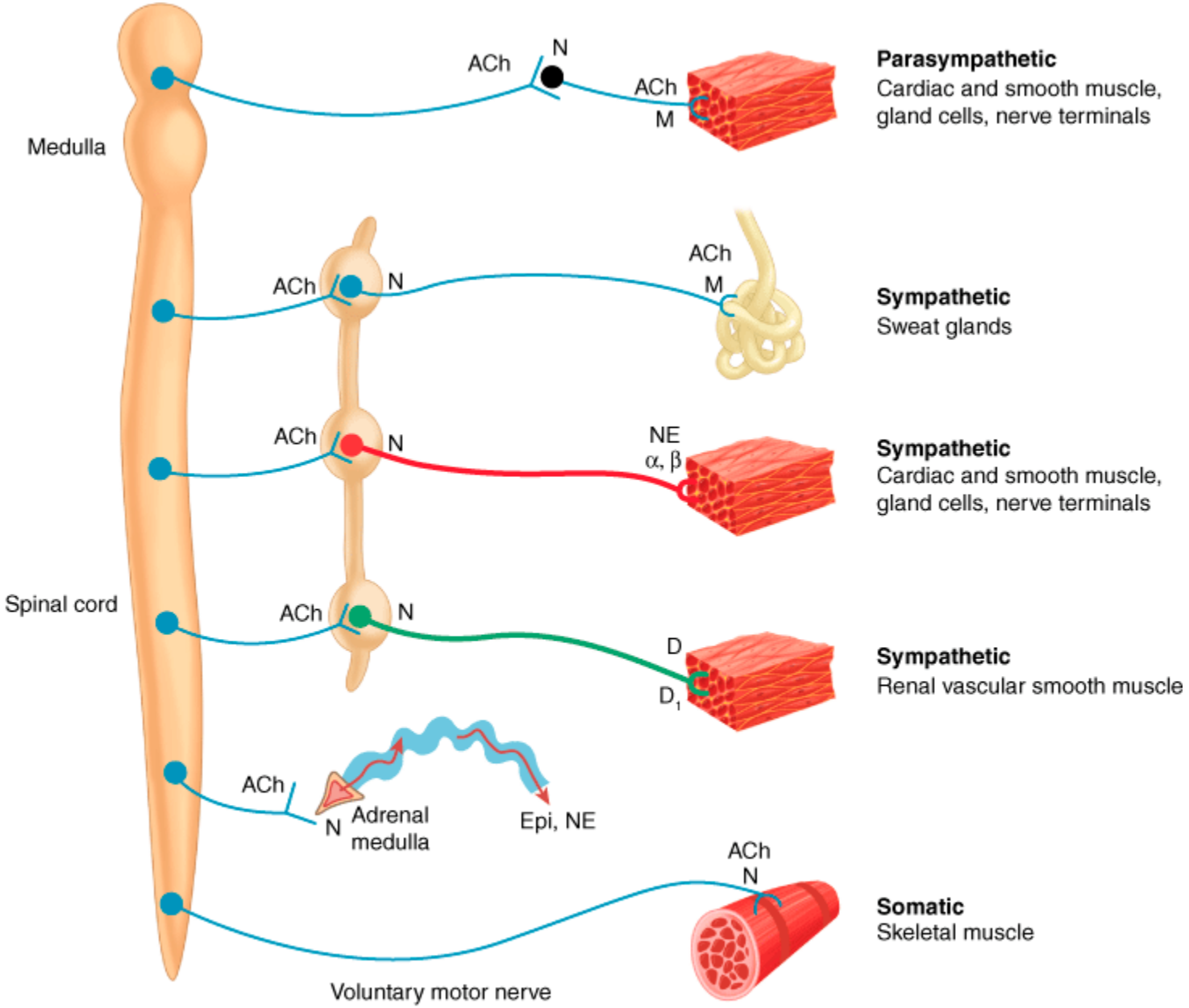


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

II. MUSCARINIC (*M*) RECEPTORS

- These receptors, in addition to:
  - binding acetylcholine,
  - also recognize muscarine,
  - but show a weak affinity for nicotine

- These receptors have been found in:
  - The CNS
  - Organs innervated by parasympathetic nerves
  - Those tissues innervated by postganglionic sympathetic cholinergic nerves (sweat glands)

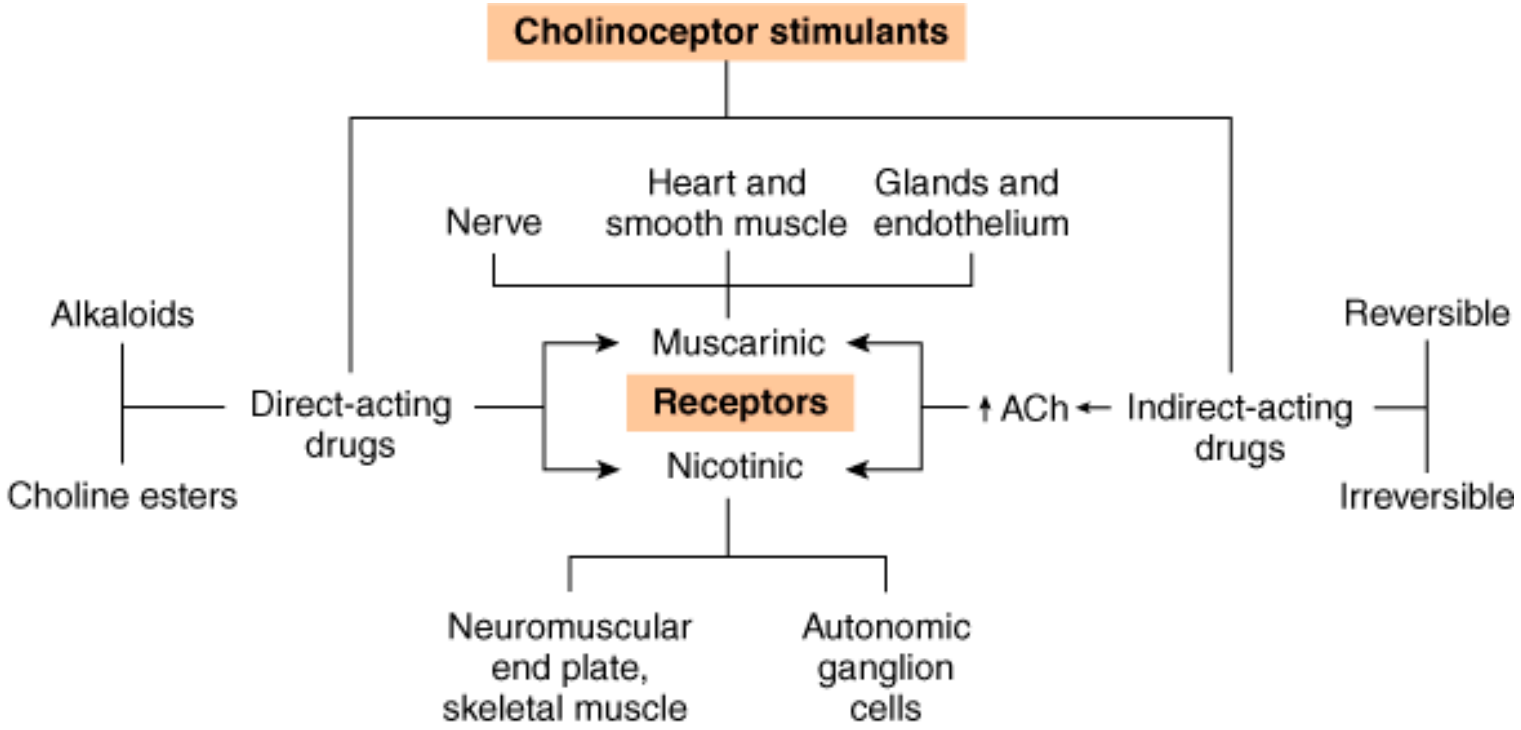


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

OVERVIEW

- *Cholinomimetics* are classified by their mechanism of action because some
  - bind **directly** to (**and activate**) **cholinoceptors**,
  - others act indirectly by **inhibiting** the **hydrolysis** of **endogenous acetylcholine**

- Cholinoceptor stimulants are also classified pharmacologically by their spectrum of action, depending on the type of receptor—muscarinic or nicotinic—that is activated



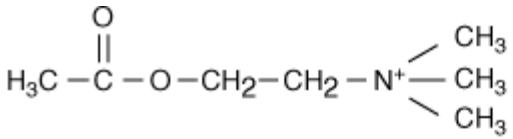
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

DIRECT ACTING CHOLINERGIC STIMULANTS

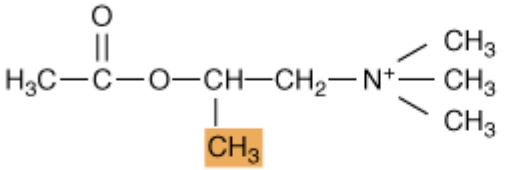
DIRECT ACTING CHOLINERGIC STIMULANTS

- Can be divided into two groups:
  - Esters of choline:
    (*Ach, methacholine,carbachol, bethanechol)*
  - Alkaloids: (*muscarine, nicotine, pilocarpine, lobeline)*
- All of the direct-acting cholinergic drugs have:
  - longer durations of action than Ach
  - and are more selective

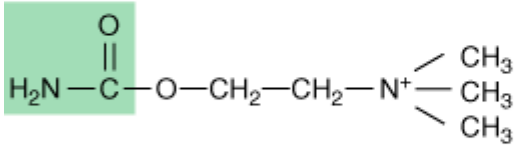
CHOLINE ESTERS



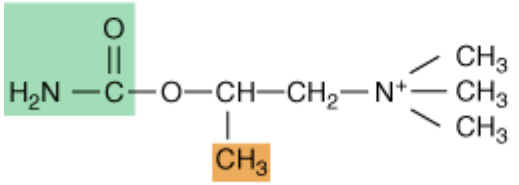
Acetylcholine



Methacholine
(acetyl-β-methylcholine)



Carbachol
(carbamoylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

- Esters of choline are permanently charged and **relatively insoluble in lipids** (**quaternary ammonium** group)

1. Ach
2. Methacholine
3. Carbachol (carbamic acid ester)
4. Bethanechol (carbamic acid ester)

- **The β-methyl** group (methacholine, bethanechol) **reduces the potency** of these drugs at **nicotinic receptors**

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

DIRECT ACTING CHOLINERGIC STIMULANTS
PHARMACOKINETICS

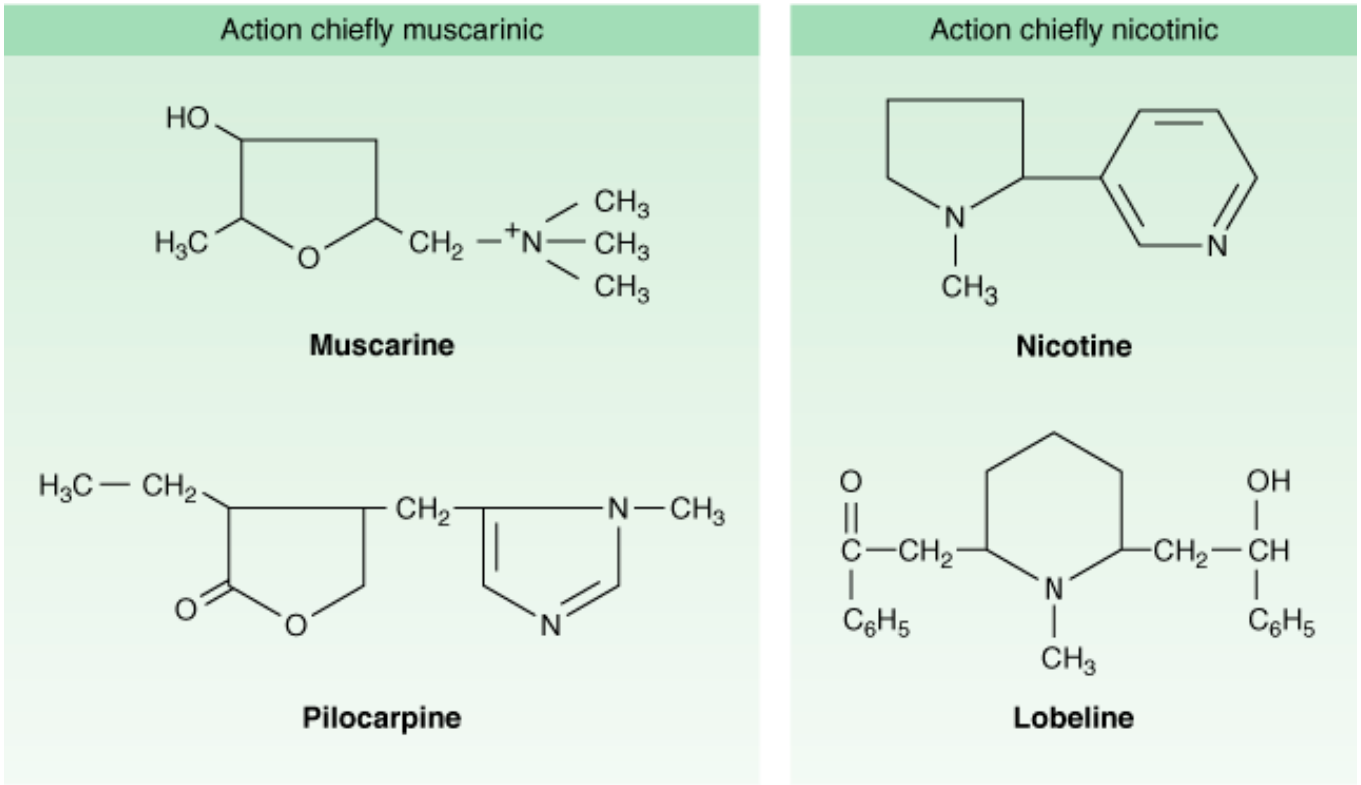
I. Choline esters

- Poorly absorbed and
- poorly distributed into the CNS because they are hydrophilic and
- susceptible to esterase hydrolysis in the GIT

- Acetylcholine is very **rapidly hydrolyzed** (A short duration of action of 5-20 seconds following a large I.V bolus)

- **Methacholine** is more resistant to hydrolysis, and the carbamic acid esters **carbachol and bethanechol** are still more **resistant to hydrolysis by cholinesterase** and have correspondingly **longer durations of action**

CHOLINOMIMETIC ALKALOIDS



DIRECT ACTING CHOLINERGIC STIMULANTS
PHARMACOKINETICS

II. Natural cholinomimetic alkaloids

- **Tertiary amines** (pilocarpine, nicotine, lobeline) are
  - **well absorbed** from most sites of administration,
  - and it **can cross the BBB**

- **Quaternary amine** (Muscarine) is
  - **less completely absorbed** from the GIT than the tertiary amines
  - but is **toxic when ingested** and it even **enters the brain**

DIRECT ACTING CHOLINERGIC STIMULANTS

- **Methacholine**, **bethanechol**, and **pilocarpine**
  - are **selective agonists of M** receptors

- Carbachol and ACh can activate both M and N receptors:
  - at **usual therapeutic doses**, the **effects of carbachol and ACh** are **entirely** due to the **activation of M** receptors b/c of:
    - **greater accessibility** and **abundance** of **the M** receptors compared with the N receptors

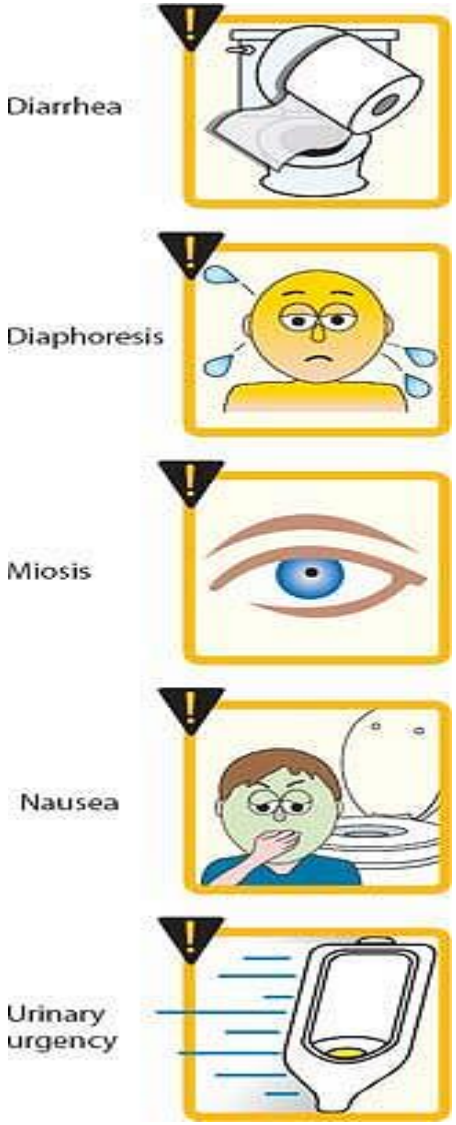
PHARMACOLOGY OF ACETYLCHOLINE-LIKE AGONISTS

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Carbachol	Negligible	++	+++
Methacholine	+	+++	None
Bethanechol	Negligible	+++	None
Muscarine	Negligible	+++	None

DIRECT ACTING CHOLINERGIC STIMULANTS

ORGAN SYSTEM EFFECT

- Most of the direct organ system effects of muscarinic cholinoceptor stimulants are readily predicted from a knowledge of the effects of parasympathetic nerve stimulation and the **distribution of muscarinic receptors**

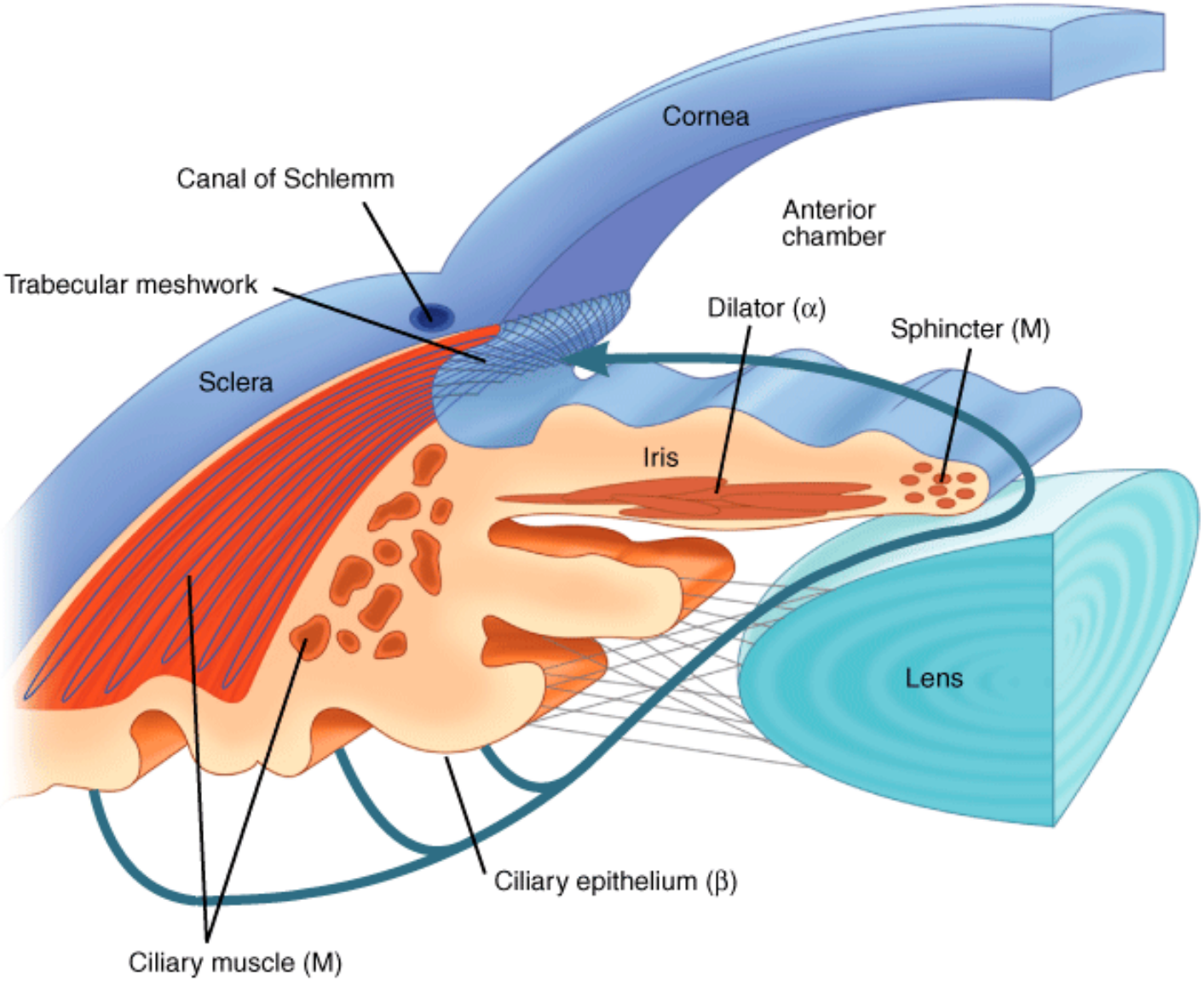


A. EYE

- Muscarinic agonists cause **contraction** of the **smooth muscle** of the:
  - Iris sphincter → miosis (contraction of pupil)
  - Ciliary muscle → resulting in accommodation of the eye for near vision http://www.youtube.com/watch?v=p_xLO7yxg0k
- These effects are mediated by the activation of **M3** receptors

Note: Both effects:

- facilitate the outflow of aqueous humor into the canal of Schlemm,
- and decrease intraocular pressure (IOP)



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

http://en.wikipedia.org/wiki/File:Eye_dilate.gif

B. CARDIOVASCULAR SYSTEM

- ACh has four primary effects on the cardiovascular system:
  a) Vasodilation*
  b) Decrease in heart rate (negative chronotropic effect)**
  c) Decrease in the conduction velocity in the atrioventricular (AV) node (negative dromotropic effect)**
  d) Decrease in the force of cardiac contraction (negative inotropic effect)**

* activation of endothelial M_3 (Increase cGMP)

** activation of M_2 receptors

B. CARDIOVASCULAR SYSTEM

- This result in:
  - marked reduction in peripheral vascular resistance,
  - bradycardia,
  - and decrease AV node conduction velocity
  - in addition to **hypotension**

- This direct slowing effect is often **opposed** by **reflex sympathetic discharge**, elicited by the decrease in blood pressure

- The net effect on heart rate depends on:
  - **local** concentrations of the agonist in the heart and in the vessels
  - and on the l**evel of reflex responsiveness**

C. Respiratory system*

- **Contraction of the smooth muscle** of **bronchial tree (bronchoconstriction)**
- **Stimulation of tracheobronchial secretion**

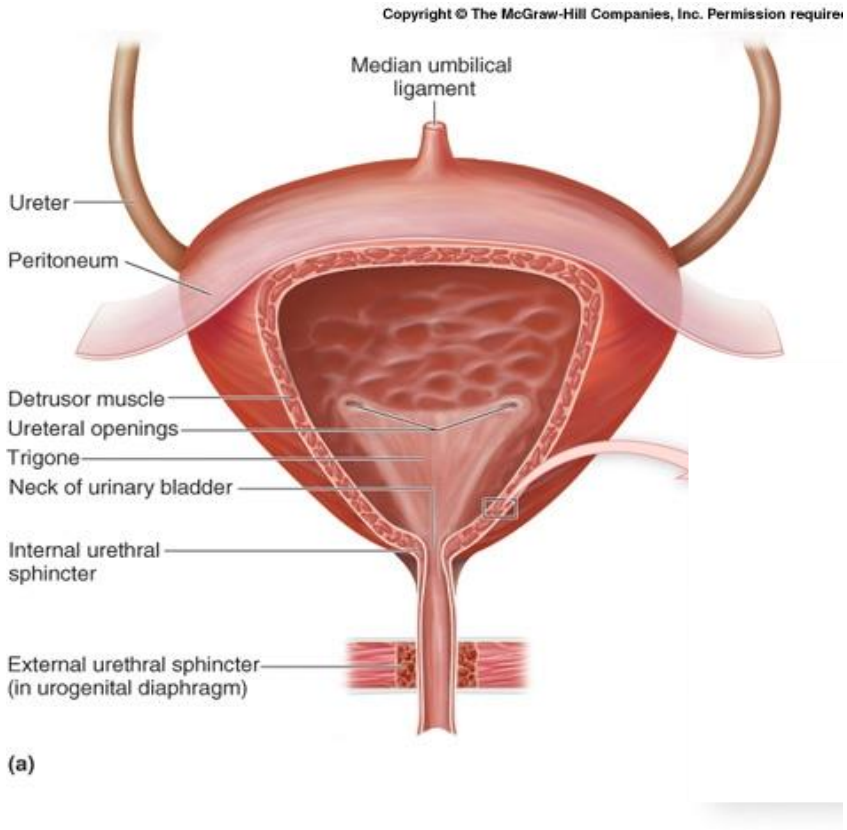
D. GIT**

- Increases the secretory and motor activity of the gut
- **Salivary and gastric glands** are **strongly stimulated**
- Pancreas and small intestinal glands are also stimulated to a lower degree
- **Most sphincters are relaxed**

- * M3 activation **M2 and M3 activation

E. Genitourinary tract

- stimulation of **detrusor** muscle **(M3** activation)
- and relaxation of **trigone and sphincter** muscles of the **bladder(M2 activation**)
  - promoting urination (voiding)



Note: human uterus is **not notably sensitive** to **muscurinic agonists**

F. Miscellaneous Secretory Glands

- Increase secretion of:
  - sweat,
  - lacrimal,
  - and nasopharyngeal glands
- Mediated by **M3** activation

G. CNS

- Contains **both muscarinic and nicotinic** receptors (brain richer in muscarinic sites, spinal cord in nicotinic)

- Activation of **M1-receptors** in the **brain** areas involved in **cognition**
- Activation of **M2R** **cause** **tremor**, **hypothermia**, **antinociception**
- Activation of **M3R** **increase appetite** and **increase body fat mass**

G. CNS:

- **Chronic exposure** to **nicotine** **increases** release of **dopamine** in the **mesolimbic system**
  - **mild alerting** action and the **addictive** property of **nicotine** absorbed **from tobacco**

- At **high concentrations**, **nicotine induces:**
  - tremor,
  - emesis,
  - and stimulation of the respiratory center

- At still **higher levels**, causes convulsions, which may terminate in fatal coma (readily absorbed…insecticide)

H. PNS:

- **Autonomic ganglia** are important sites of **nicotinic synaptic action (N_N)**
- **Activation of nicotinic receptors** initiate **AP** in **postganglionic neurons**
  - (both **parasympathetic** and **sympathetic**)
- In **CVS**, the effects of nicotine are chiefly **sympathomimetic**:
  - **hypertension** and **sympathetic tachycardia**
  - **may alternate** with a **bradycardia** mediated by **vagal discharge**
- In the **GIT** and **UT**, the effects are largely **parasympathomimetic**: nausea, vomiting, diarrhea (N,V,D), and voiding of urine
- **Prolonged exposure may result in depolarizing blockade of the ganglia**

I. Neuromuscular Junction (N_M)

- When a **nicotinic agonist** is **applied directly** to a **NMJ,**
  - an **immediate depolarization** of the end plate results,
  - causing **muscle contraction**

- **Depolarizing nicotinic** agents **that are not rapidly hydrolyzed** (**like nicotine itself**) cause **rapid** development of **depolarization blockade.**

  - Transmission blockade persists even when the membrane has repolarized (flaccid paralysis)

INDIRECT ACTING CHOLINOMIMETICS

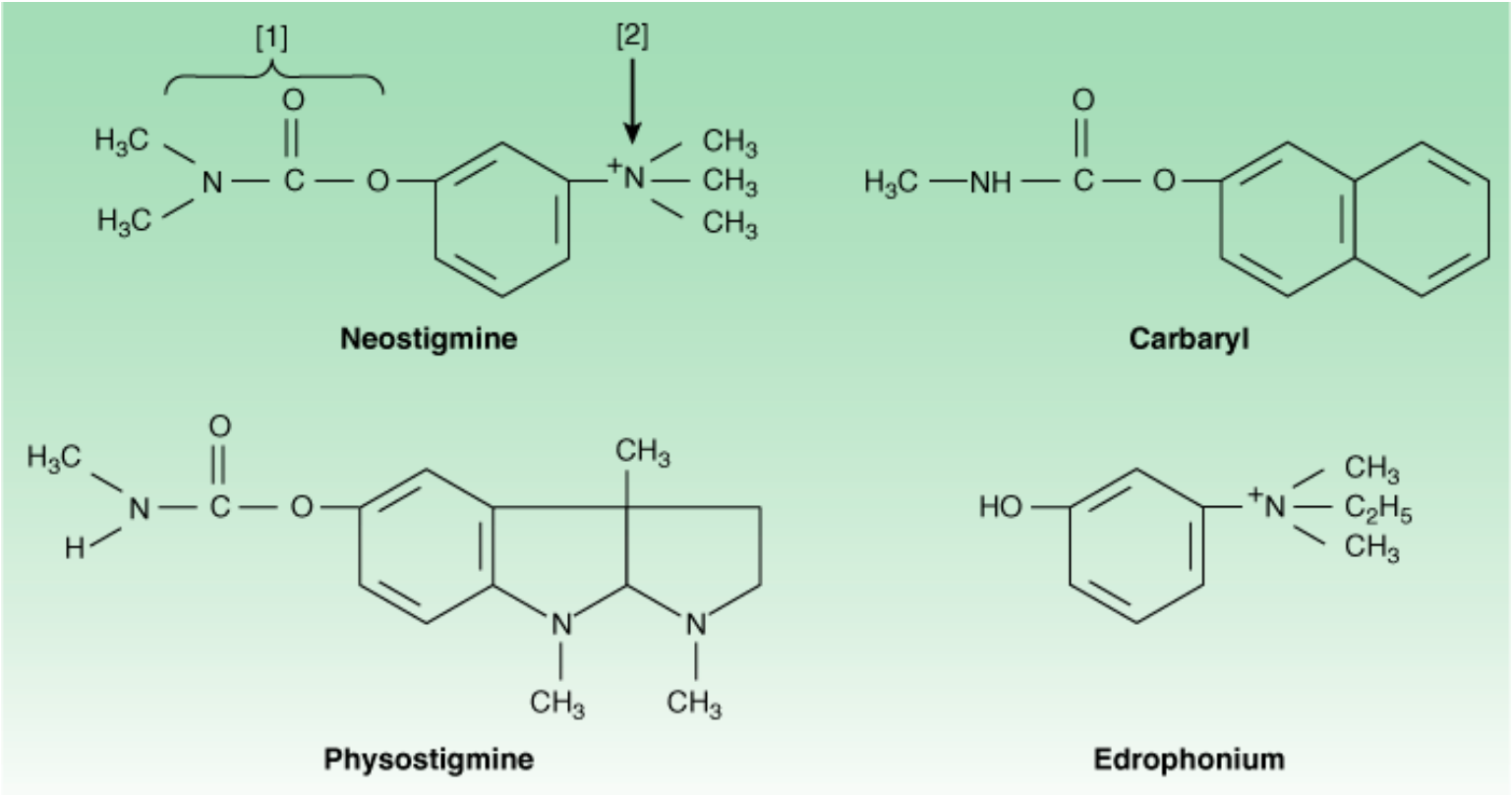
INDIRECT ACTING CHOLINOMIMETICS

- There are **three chemical groups** of **cholinesterase inhibitors:**

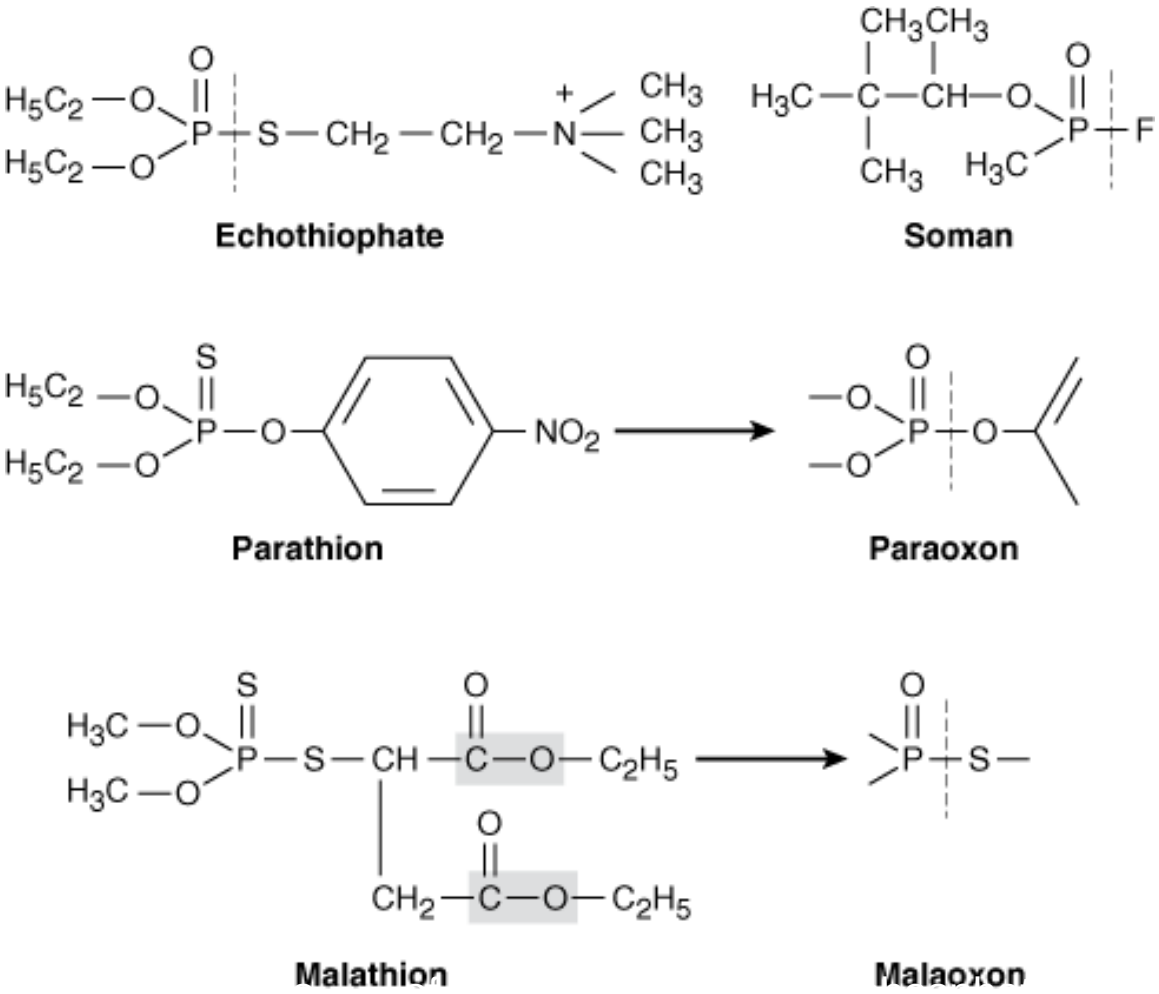
(1) **Simple alcohols bearing a quaternary ammonium group**, eg, edrophonium

(2) **Carbamates:** carbamic acid esters of alcohols having quaternary or tertiary ammonium groups (eg, neostigmine, physostigmine)

(3) **Organophosphates:** organic derivatives of phosphoric acid (eg, echothiophate)



- **Absorption of** the **quaternary** c**arbamat**es is n**egligible** as well as **CNS distribution**
- **Physostigmine** is **well absorbed** from **all site** and **can be used topically**



INDIRECT ACTING CHOLINOMIMETICS
PHARMACOKINETICS

Organophosphate cholinesterase inhibitors:

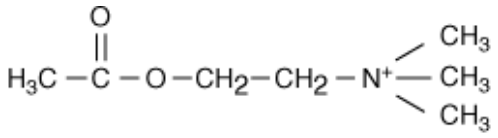
- The **thiophosphate** insecticides:
  - parathion, malathion, and related compounds
  - are rapidly absorbed by all routes

- **Malathion** (but not parathion):
  - is **rapidly metabolized** by other pathways to **inactive products** in **birds** and **mammals,**
  - but **not in insects**;
  - **safe enough** for sale to general public

INDIRECT ACTING CHOLINOMIMETICS
MECHANISM OF ACTION

- AchE is the primary target of these drugs, but butyrylcholinesterase is also inhibited

- The active site of AChE comprises two distinc
  - an *anionic site*
  - and an *esteratic site*



Acetylcholine

- 1st step: **ACh binds** to the enzyme's **active site** and **is hydrolyzed,** yielding **free choline** and the acetylated enzyme

- 2nd step, the **covalent acetyl-enzyme bond** is **split**, with the addition of **water** (hydration)

- The **entire** process takes place in approximately **150 microseconds**

INDIRECT ACTING CHOLINOMIMETICS
MECHANISM OF ACTION

- **Anti-cholinesterase drugs** fall into **three main** groups according to the nature of their interaction with the active site:

I. **Short acting anticholinesterase (quaternary alcohols , e.g. edrophonium):**

- **Reversibly** bind **electrostatically** and by **hydrogen bonds** to the active site,
  - thus **preventing access of ACh (competitive inhibition)**

- The **enzyme-inhibitor complex** does **not** involve a **covalent** bond and is correspondingly **short-lived** (on the order of **2-10 minutes**)

INDIRECT ACTING CHOLINOMIMETICS
MECHANISM OF ACTION

II. **Medium-duration anticholinesterase (e.g. Neostigmate, pyridostigmate, and physostigmine):**

- They undergo a two-step hydrolysis sequence analogous to that for Ach

- The covalent bond of the *carbamoylated* enzyme is considerably more resistant to the second (hydration) process,
  - and this step is correspondingly prolonged (on the order of 30 minutes to 6 hours)

INDIRECT ACTING CHOLINOMIMETICS
MECHANISM OF ACTION

III. **Irreversible anticholinesterases (synthetic organophosphate compounds):**

- They undergo **initial binding** and **hydrolysis** by the enzyme, resulting in a *phosphorylated* active site

- The covalent phosphorus-enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours)

- Phosphorylated enzyme may undergo ***aging:***
  - breaking one of the oxygen-phosphorus bonds of the inhibitor,
  - further strengthening the phosphorus-enzyme bond
  - and making it impossible for chemical reactivation

INDIRECT ACTING CHOLINOMIMETICS
MECHANISM OF ACTION

Cholinesterase regenerator:

- **Strong nucleophiles** like **pralidoxime:**
  - are able **to split** the **phosphorous-enzyme bond** and can be used in **reversal** of **organophosphate insecticide poisoning (before aging)**

- **Once aging has occurred**,
  - the enzyme-inhibitor complex is even more stable and is more difficult to break, even with oxime regenerator compounds

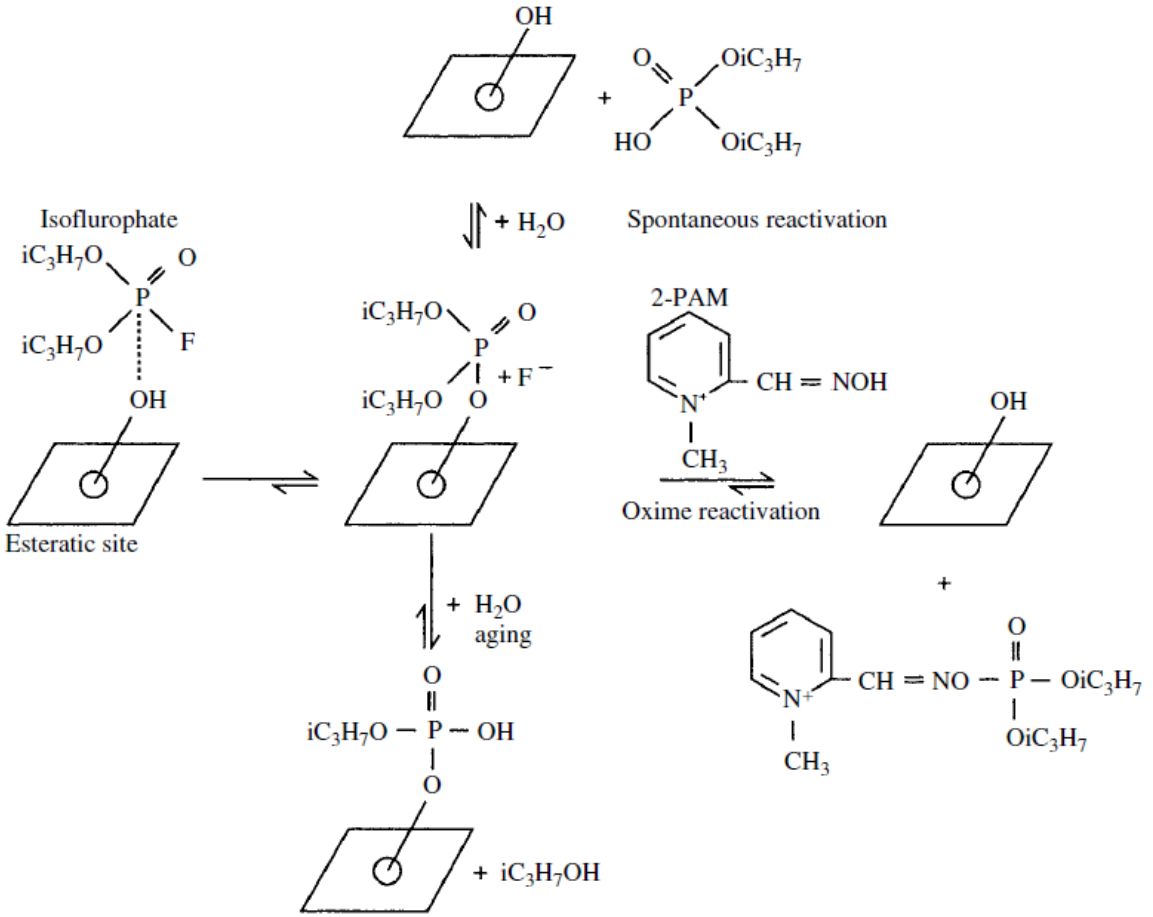


FIGURE 12.4

Isofluorophate reaction at AChE esteratic site, aging, spontaneous reactivation, and oxime reactivation. *Left,* the nucleophilic attack on the phosphorus of isofluorophate by the serine oxygen. This results in a stable phosphorylated enzyme intermediate, which undergoes dephosphorylation at a negligible rate (*top*). A more favorable reaction is the loss of an isopropoxy group, a process termed aging (*bottom*). This renders the phosphorylated enzyme resistant to dephosphorylation by an oxime. The original phosphorylated intermediate (*center*) will react with the nucleophilic oxygen of pralidoxime (2-PAM), resulting in dephosphorylation of the enzyme and formation of an oxime phosphonate (*lower right*).

INDIRECT ACTING CHOLINOMIMETICS
ORGAN SYSTEM EFFECT

a. **Central nervous system (CNS)**

- At ***low concentrations***, the ***lipid-soluble*** *cholinesterase inhibitors* cause:
  - *activation* on the *electroencephalogram*
  - and a *subjective alerting* response.

- At **higher concentrations**, cause
  - **generalized convulsions**,
  - which may be **followed by coma and respiratory arrest.**

b. **Eye, Respiratory Tract, GIT, & Urinary Tract???**

INDIRECT ACTING CHOLINOMIMETICS
ORGAN SYSTEM EFFECT

c. Cardiovascular system

- The actions of anticholinesterase agents on the CV system are complex

- The cholinesterase inhibitors can **increase** activity in both **sympathetic and parasympathetic ganglia supplying the heart**

- and at the acetylcholine receptors on neuroeffector cells (cardiac and vascular smooth muscles) that receive cholinergic innervation

c. Cardiovascular system

- **Heart:** parasympathetic effects predominate (negative chronotropic, inotropic and dromotropic, **decrease in cardiac output** and **blood pressure**)

- **Vascular smooth muscle:** cholinesterase inhibitors have minimal effects (most vascular beds lack cholinergic innervation)

- …..**increase in systemic vascular resistance** and **blood pressure** that is initiated **at sympathetic ganglia**

- **Net cardiovascular effects:**
  - modest bradycardia,
  - decrease CO,
  - increase in BP

- **Toxic doses:** more marked bradycardia (occasionally tachycardia) and hypotension

d. Neuromuscular junction

- **Neuromuscular transmission** in **skeletal muscle** is:
  - **enhanced** by **low concentrations** of anticholinesterase agents,
  - whereas **high concentrations** result **in fibrillation** of muscle fibers

- With **marked inhibition of AchE**,
  - depolarizing neuromuscular blockade occurs;

- **Neostigmine**: additional direct nicotinic agonist effect at the NMJ;
  - effective in the therapy of **myesthenia gravis**

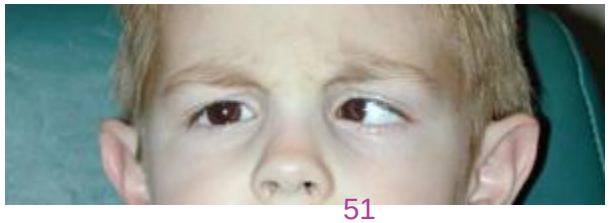
CLINICAL USES OF THE CHOLINOMIMETICS

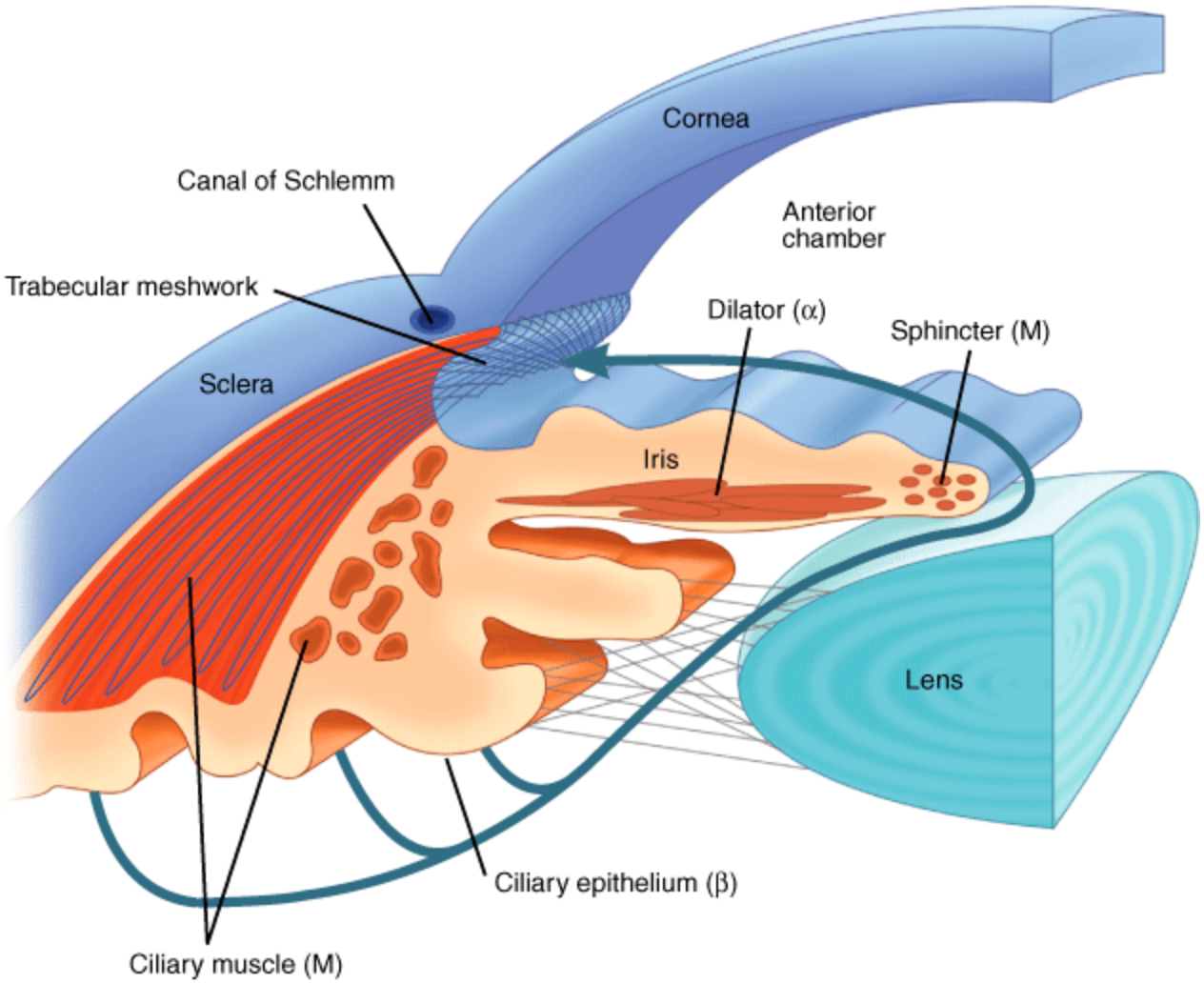
a. Glaucoma

- In the **past**, glaucoma was treated **with either:**
  - direct agonists (pilocarpine, methacholine, carbachol)
  - or cholinesterase inhibitors (physostigmine, demecarium, echothiophate, isoflurophate)

- For chronic glaucoma, these drugs have been largely replaced by topical:
  - β-blockers
  - and prostaglandin derivatives

- **Accommodative esotropia** (strabismus caused by accommodative error) in young children is sometimes **diagnosed** and **treated** with **cholinomimetic agonists**





Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

CLINICAL USES OF THE CHOLINOMIMETICS

a. Glaucoma

- ***Acute angle-closure glaucoma***:
  - a medical emergency
  - that is frequently treated initially with drugs
  - but usually requires surgery for permanent correction

- Initial therapy:
  - often consists of a combination of:
    - a direct muscarinic agonist
    - **and** a cholinesterase inhibitor
    - (eg, pilocarpine plus physostigmine)

- Once the intraocular pressure is controlled and the danger of vision loss is diminished,
  - the patient can be prepared for corrective surgery (iridectomy)

- ***Open-angle glaucoma***: **chronic diseases** that are not amenable to traditional surgical correction, (now laser techniques available!!!)

CLINICAL USES OF THE CHOLINOMIMETICS

b. Gastrointestinal and Urinary Tracts

- **In depression of smooth muscle activity without obstruction**,
- direct or indirect cholinomimetic with muscarinic effects may be helpful in:
  1. **postoperative ileus** (atony or paralysis of the stomach or bowel following surgical manipulation)
  2. **congenital megacolon**
  3. **Urinary retention**
     1. postoperatively or
     2. postpartum or
     3. secondary to spinal cord injury
     4. or disease (neurogenic bladder)
  4. sometimes used to **increase the tone** of **the lower esophageal sphincter** in patients with **reflux esophagitis**

CLINICAL USES OF THE CHOLINOMIMETICS

b) Gastrointestinal and Urinary Tracts

- Of the choline esters,
  - **bethanechol** is the most widely used for these disorders

- Of the cholinesterase inhibitors,
  - **neostigmine** is the most widely used for these applications

- **Pilocarpine** has long been used to increase salivary secretion

- **Cevimeline:** a new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome (dry mouth and eyes)

CLINICAL USES OF THE CHOLINOMIMETICS

C. Neuromuscular Junction

1. **Myasthenia gravis**: an autoimmune disease affecting skeletal muscle (antibodies are produced against the nicotinic receptor)

   Symptoms:

   1. ptosis (lazy eye),
   2. diplopia,
   3. difficulty in speaking and swallowing,
   4. and extremity weakness
   5. (in extreme cases may interfere with respiration)

- **Cholinesterase inhibitors—but not direct-acting acetylcholine receptor agonists—are used**

Edrophonium is sometimes used as a diagnostic test!

- (A **2 mg dose** is injected **IV** after baseline muscle strength has been measured. If **no reaction** occurs **after 45 seconds**, an additional **8 mg** may be **injected)**.
- An improvement in muscle strength that lasts about 5 min. will usually observed in myesthenia gravis

CLINICAL USES OF THE CHOLINOMIMETICS

c. Neuromuscular Junction

- **Long-term therapy: pyridostigmine; neostigmine or ambenonium:**
  - require **frequent dosing**
  - (every **6 hours** for **pyridostigmine and ambenonium**
  - and **every 4 hours** for **neostigmine**)

- **Sustained-release** preparations should be used **only at night** and **if needed**

- **Longer-acting cholinesterase inhibitors ARE NOT USED**,
  - because the **dose requirement** in this disease **changes too rapidly** to permit **smooth control of symptoms** with long-acting drugs

- **Immunosuppressant drugs and thymectomy are also used**

CLINICAL USES OF THE CHOLINOMIMETICS

c. Neuromuscular Junction

- Muscarinic effects (of therapy)
  - (abdominal cramps, diarrhea, increased salivation, miosis, bradycardia etc)
  - can be controlled by the administration **of atropine**

2. To reverse neuromuscular blockade after surgery:

- **Neuromuscular blockade** is frequently produced as an adjunct to **surgical anesthesia**, using ***nondepolarizing*** **neuromuscular relaxants** such as pancuronium and newer agents
- **neostigmine and edrophonium** are the drugs of choice (I.V or I.M)

CLINICAL USES OF THE CHOLINOMIMETICS

d. **Antimuscarinic Drug Intoxication** (atropine, tricyclic antidepressants)

- **Physostigmine** has been used for this application,
  - because it enters the central nervous system and **reverses the central**
  - as well as the **peripheral signs** of muscarinic blockade

- However, can produce **dangerous central nervous system effects**....just in severe cases!

CLINICAL USES OF THE CHOLINOMIMETICS

e. CNS (Alzheimer's Disease)

- **Tacrine, donepezil, galantamine, & rivastigmine** are **approved** for:
  - the **palliative** treatment of Alzheimer's disease

- These agents can **cross the BBB** to produce a **reversible inhibition** of AChE in the CNS

- They produce modest but **significant improvement** in the **cognitive function** of patients with mild to moderate Alzheimer's disease,
  - but **they do not delay progression** of the disease

- **Hepatic toxicity** is **significant** with **tacrine**

TOXICITY

A. **Direct-Acting Muscarinic Stimulants** (pilocarpine, and the choline esters)

- **Overdosage** is characterized by **exaggeration** of the various **parasympathomimetic effects**:
- nausea, vomiting, diarrhea (N,V,D)
- salivation,
- sweating,
- urinary urgency,
- hypotension with reflex tachycardia,
- bronchial constriction
- Resembles that produced by consumption of mushrooms of the **genus *Inocybe***
- ***Tx: Atropine***

TOXICITY

B. Direct-Acting Nicotinic Stimulants (nicotine)

ACUTE TOXICITY: the fatal dose of nicotine is ~40 mg, or 1 drop of the pure liquid (contents of two regular cigarettes)

- Ingestion of nicotine by infants or children is
  - usually followed by **vomiting,**
  - **limiting** the amount of the **alkaloid absorbed**
- Nicotine is also used in a number of **insecticides**
- less important than ***CHRONIC NICOTINE TOXICITY*** "cigarette smoking"

- **Several approaches to help patients stop smoking:**

Replacement therapy with nicotine (gum, transdermal patch, nasal spray, or inhaler)

- have **low abuse potential** and **are effective**
- Their **action** derives from **slow absorption of nicotine**
- and **reduces the desire to smoke**

Varenicline: a recently approved drug for smoking cessation

- It is a synthetic drug with **partial agonist** action at **nicotinic receptors**
- **its use is limited by**
  - **nausea, insomnia** and **exacerbation** of **psychiatric illnesses**, including **anxiety and depression.**
- **Suicidal ideation** has also been reported in some patients

TOXICITY

c. Cholinesterase inhibitor:

- The major source is **pesticide** use in agriculture & at home
- The dominant initial signs are those of **muscuranic excess** (salivation, miosis, sweating…) (**acute toxicity**)
- and **depolarizing neuromuscular blockade** (peripheral nicotinic effect).
- **Therapy:**
  1. maitanance **of vital sign** – respiration in particular
  2. **decontamination** – removal of cloths and washing the skin in case of dusts and sprays
  3. **atropine** parenterally
  4. **Pralidoxime**.

Chronic exposure to certain **organophosphate** compounds causes n**europathy** associated with **demyelination of axon**