Chapter 7

Cholinoceptor-activating drugs
Objectives

- To know classification of cholinocceptor-activating and cholinesterase-inhibiting drugs, chemical structures and mechanism of action
- To understand major pharmacological effects and therapeutic applications
- To understand major adverse reactions
Cholinergic nerves and receptors

Brain
Spinal cord
Somatic
Sympathetic
Parasympathetic

Ganglia

Adrenal medulla

Effector organs

Skeletal muscle
Sweat gland and skeletal muscle vessels
Smooth muscle
Heart
Gland

Cholinergic nerve
transmitter
Noradrenergic nerve
Efferent Nervous System

ACh
NA
Acetylcholine receptor

- **Muscarinic acetylcholine receptors**
  - $M_1$  $M_2$  $M_3$  $M_4$  $M_5$
  - Gq protein, Gi protein

- **Nicotinic acetylcholine receptors**
  - $N_m$  $N_n$  ion–gated channel
Classification of drugs

Cholinomimetic agents

\{ 
Cholinceptor-activating (direct) 
Cholinesterase inhibitors (indirect) 
\}
I. The direct-acting drugs

Chemistry & pharmacokinetics

A. Chemical structures:

Esters of choline: acetylcholine, methacholine, carbacholine…

Alkaloids: muscarine, nicotine

• M,N receptor agonists: acetylcholine, carbacholine

• M receptor agonists: pilocarpine
Absorption, distribution, Metabolism

- Choline esters: poorly absorbed, poor in CNS--hydrophlic
- Alkaloids: easy to absorbed, nicotine > muscarine --- neurotoxic (mushrooms)
Pharmacological effects

1. Eyes
   (1) miosis (M₃-R)
   (2) reduced intraocular pressure
      (secondary effect)
   (3) accommodation spasm (M₃-R)
2. Miscellaneous secretary glands (M₃-R)
   sweat, salivary, nasopharyngeal glands

3. Respiratory system
   (1) contract smooth muscle in bronchial tree (M₃-R)
   (2) stimulate secretion of tracheobronchial mucosa (M₃-R)
4. Cardiovascular system

(1) Reduce peripheral vascular resistance (vasodilation)
(2) Changes heart rate

Muscarinic agonist → atrial muscle

$K^+$ → sinoatrial muscle

→ atrioventricular nodes

→ hyperpolarization-activated current

→ slow inward calcium current
Vasodilation and blood pressure

$M_3 R$ in endothelial cells $\rightarrow$ relax smooth muscle

NO $\rightarrow$ guanylyl cyclase $\rightarrow$ cGMP
5. Gastrointestinal (GI) tract

(1) Secretion of salivary (M₃-R), gastric (M₁-R), gut glands (M₃-R)

(2) Motility of GI smooth muscle (M₃-R)

(3) Sphincters of GI → relaxation
6. Genitourinary tract ($M_3$-R)

Contraction of detrusor urinary

Relaxation of trigone and sphincter muscles of the bladder

To promote voiding

Uterus is less sensitive to $M$-receptor agonists
Toxic reactions

overdose muscarinic drugs:
1. nausea
2. vomiting
3. diarrhea
4. salivation
5. sweating
6. cutaneous vasodilation
7. bronchial construction
Clinical uses

Glaucoma:
  angle-closure glaucoma
  open-angle glaucoma
  some cases of secondary glaucoma
Postoperative ileus:
Stomach, bowel, urine retention:
  (bethanechol)
Salivary secretion:
  (pilocaine)
Pilocarpine

Saliva, and perspiration

Pressure within the eye

Contraction of the pupil

loosen adhesion between iris and lens

Treatment of glaucoma

Treatment of iritis

Counteracting the mydriatic and cycloplegic action (atropine and ganglion-blocking agents)
Nicotinic drugs:
40mg—fatal dose
Acute toxic effects:
1. convulsion, coma, respiratory arrest
2. hypertension/ cardiac arrhythmias
Π. The indirect-acting drugs

(anticholinesterase agents, such as neostigmine, physostigmine)
Pharmacodynamics

A. Mechanisms of Action

\[
\text{acetylcholine} \xrightarrow{\text{acetylcholinesterase}} \text{choline} + \text{acetic acid}
\]

Indirect-acting drugs

amplify endogenous acetylcholine
B. Pharmacological actions

- Similar to that of the direct-acting drugs on the eye, the cardiovascular and gastrointestinal systems, and the skeletal muscle neuromuscular junction.
Clinical uses

1. Myasthenia gravis

   Autoimmune disease---antibodies diminish nicotinic receptors

   Neostigmine, pyridostigmine, ambenonium
2. paralytic ileus and atony of urinary bladder
   neostigmine
3. antimuscarinic drug intoxication
   physostigamine (counteracting atropine and tricyclic antidepressants)
4. glaucoma
   physostigamine
Adverse reaction

Similar to those of the direct-acting agents: salivation, sweating, cutaneous vasodilation, bronchial construction.