Cholinergic Drugs

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Cholinergic Drugs

Cholinomimetics:

1. **Acetylcholine receptor stimulants**

- **Agonists that stimulate acetylcholine muscarinic and nicotinic receptors.**
- **Muscarinic receptors are located on smooth muscle, heart & exocrine glands**
- **Nicotinic receptors are located in autonomic ganglia.**

Cholinergic Drugs

2. **Cholinesterase inhibitors:**

- **Drugs which inhibit the hydrolysis of acetylcholine leading to its accumulation at its receptors.**
- **The excess acetylcholine stimulates cholinoceptors (not selective) to evoke increased response.**

Direct-Acting Cholinomimetics

1) **Choline esters: Acetylcholine, Methacholine.**
2) **Alkaloids (naturally occurring): Muscarine, Pilocarpine.**

Pharmacokinetics:

- **Choline esters are quaternary ammonium compounds, charged, highly water soluble and insoluble in lipids.**
- **They are poorly absorbed and poorly distributed into most tissues.**

Direct-Acting Cholinomimetics

- **They are hydrolyzed in the GIT and not active by the oral route.**
- **The tertiary natural cholinomimetic alkaloid pilocarpine is well absorbed from most sites of administration.**
- **The alkaloid muscarine is a quaternary amine and is less completely absorbed from GIT than tertiary amines but is toxic when ingested.**

Direct-Acting Cholinomimetics

Pharmacodynamics:

- **Most of the direct organ-system effects of cholinomimetics can be predicted from knowledge of the effects of parasympathetic nerve stimulation and the distribution of muscarinic receptors.**

Direct-Acting Cholinomimetics

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, veins	Dilation (via EDRF). Constriction (high-dose direct effect)

Direct-Acting Cholinomimetics

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

EDRF, endothelium-derived relaxing factor.

*Only the direct effects are indicated; homeostatic responses to these direct actions may be important (see text).

Direct-Acting Cholinomimetics

Eye: [M_3 receptors]

1. **Contraction of the smooth muscle of the iris sphincter → miosis, pupillary constriction.**
2. **Contraction of the ciliary muscle → accommodation for near vision.**
3. **Facilitation of aqueous humor outflow, which reduces intraocular pressure.**

Direct-Acting Cholinomimetics

Cardiovascular System [M_2 receptors]:

1. **Reduction of heart rate → bradycardia (negative chronotropy)**
2. **Decreased AV node conduction velocity (negative dromotropy)**
3. **Decreased contractility of atrial muscle (negative inotropy), and decreases its refractory perioid**
4. **Effects on ventricles are negligible**

Direct-Acting Cholinomimetics

5. **Stimulation of M_3 and M_5 receptors in the endothelium of blood vessels increases the synthesis and release of endothelium-dependent relaxing factor (EDRF) which mediates vasodilation, and reduction of blood pressure.**

- **Cholinomimetics have NO direct effect on blood vessels because of lack of parasympathetic innervation of blood vessels**

Direct-Acting Cholinomimetics

6. **Pilocarpine (IV) has different effects on blood pressure: after the initial reduction in blood pressure, blood pressure will be elevated due to sympathetic ganglionic discharge caused by activation of M_1 receptors on sympathetic ganglia.**

Direct-Acting Cholinomimetics

Respiratory System: [M_3 receptors]

1. **Contraction of smooth muscle of the bronchial tree → bronchoconstriction**
2. **Stimulation of secretions of glands in tracheobronchial mucosa**

Direct-Acting Cholinomimetics

Gastrointestinal Tract: [M_3 receptors]

1. **Increased gastric secretions.**
2. **Peristaltic activity is increased throughout the gut and most sphincters are relaxed.**

Direct-Acting Cholinomimetics

Genitourinary tract: [M_3 receptors]

1. **Stimulation of detrusor muscle of the urinary bladder → contraction.**
2. **Relaxation of bladder sphincter.**

- **Both promote voiding (urination).**

3. **Human uterus contacts and its vessels dilate in response to muscarinic agonists, but pregnant uterus is not affected.**
4. **Erection (M receptors)**

Direct-Acting Cholinomimetics

Secretory glands: [M_3 receptors]

1. **Stimulation of secretions of salivary (M_1 also), sweat, lacrimal and nasopharyngeal glands.**

Indirect-Acting Cholinomimetics

- **Acetylcholinesterase inhibitors or anticholinesterases.**

1) **Edrophonium. Simple alcohol bearing a quaternary ammonium group.**
2) **Carbamates:**

a. **Neostigmine. (ester of carbamic acid) and is a quaternary ammonium.**

Indirect-Acting Cholinomimetics

b. **Physostigmine.** **is a naturally occurring tertiary amine (lipid soluble)**
c. **Carbaryl.** **Very high lipid solubility, it is an insecticide.**

Indirect-Acting Cholinomimetics

3. **Organophosphates:**

a. **Echothiophate (thiocholine derivative of clinical value)**

b. **Parathion, Malathion → Paraoxon, Malaoxon (Insecticides)**

c. **Soman, Sarin (nerve gases).**

Indirect-Acting Cholinomimetics

- **These Anticholinesterases have similar pharmacodynamics but differ in chemical structure and pharmacokinetics.**
- **They also affect nicotinic transmission (why?)**

Indirect-Acting Cholinomimetics

Pharmacokinetics:

- **Absorption of neostigmine (quaternary ammonium carbamates) from the conjunctiva, skin and lungs is poor.**
- **Distribution into the central nervous system (CNS) is negligible.**

Indirect-Acting Cholinomimetics

- **Physostigmine, in contrast, is well absorbed from all sites and can be used topically.**
- **It is also distributed to the CNS (why?).**
- **It is more toxic than more polar carbamates.**
- **Carbaryl is very well absorbed from all site and distributed to the CNS extensively.**

Indirect-Acting Cholinomimetics

- **The organophosphates (except echothiophate) are well absorbed from skin, lung, gut and conjunctiva. They are extensively distributed to all parts of the body including CNS.**
- **Echothiophate is highly polar and is used topically in the conjunctiva.**

Indirect-Acting Cholinomimetics

Pharmacodynamics:

- **Inhibition of cholinesterases increases the concentration of endogenous acetylcholine.**

1. **Edrophonium produces a short-lived and reversible inhibition of the enzyme (2-10 minutes).**
2. **Carbamates produce a reversible and prolonged inhibition (0.5-6 hours) .**

Indirect-Acting Cholinomimetics

3. **Organophosphates phosphorylate the active site covalently and irreversibly.**

- **The effect is long-lasting (hundreds of hours).**
- **Later on, one oxygen-phosphorus bonds is broken leading to strengthening of the phosphorus-enzyme bond, a process called aging of the enzyme (24-48 hours after exposure).**

Indirect-Acting Cholinomimetics

- **Oximes (pralidoxime) are nucleophiles and are able to break the phosphorus-enzyme bond before aging occurs, and are called "Cholinesterase regenerators".**
- **They are part of the treatment of organophosphate but not carbamate poisoning. When? & Why?**

Indirect-Acting Cholinomimetics

Organ-system effects:

- **These effects are due to accumulation of acetylcholine at all cholinergic sites.**
- **Therefore, the actions are similar, but not identical, to those of the direct-acting cholinomimetic agonists.**

1. **Actions on eye, GIT, respiratory tract and urinary tract are similar to the direct-acting cholinomimetic agonists.**

Indirect-Acting Cholinomimetics

2. **CNS (both muscarinic and nicotinic receptors):**

- **Low concentrations cause diffuse activation of CNS and an alerting response.**
- **In higher concentrations, they produce generalized convulsions followed by coma and death.**

Indirect-Acting Cholinomimetics

3. **CVS:**

- **They can stimulate both parasympathetic and sympathetic ganglia (nicotinic receptors), although parasympathetic activation predominates.**
- **Sympathetic ganglia stimulation may counteract the effects of acetylcholine on vascular beds → vasoconstriction. At toxic doses these agents may cause tachycardia, instead of bradycardia.**

Indirect-Acting Cholinomimetics

4. **Neuromuscular junction (nicotinic receptors):**

- **Low concentration increases the strength of contraction in skeletal muscle.**
- **High concentration leads to fibrillation of the muscle fibers, muscular fasciculation may also occur.**
- **Marked inhibition of acetylcholinesterase my produce neuromuscular blockade.**