

# Cholinergic Agents

Cholinergic Receptors				
Types of Receptor	Muscarinic Receptor		Nicotinic Receptor	
	Metabotropic (G protein coupled) receptor		Ionotropic (Ion channel coupled) receptor	
Effects Upon Activation	1. Activation of Phospholipase C 2. Formation of <ol style="list-style-type: none"> <li>a. Inositol Triphosphate (IP3)</li> <li>b. Diacyl Glycerol (DAG)</li> </ol> 3. Inhibition of Adenylate Cyclase <ol style="list-style-type: none"> <li>a. Activation of K<sup>+</sup> channels</li> <li>b. Closure of Ca<sup>2+</sup> channels</li> </ol>		1. Coupled with cation channels 2. Mediate fast excitatory synaptic transmission	
Subdivisions	Types	Locations	Types	Locations
	M1	<ul style="list-style-type: none"> <li>• CNS</li> </ul>	N <sub>M</sub>	<ul style="list-style-type: none"> <li>• Skeletal muscle</li> </ul>
	M2	<ul style="list-style-type: none"> <li>• CNS</li> <li>• Heart</li> </ul>	N <sub>N</sub>	<ul style="list-style-type: none"> <li>• Autonomic ganglia</li> <li>• Adrenal medulla</li> </ul>
	M3	<ul style="list-style-type: none"> <li>• CNS</li> <li>• Smooth muscle</li> <li>• Endothelium</li> <li>• Secretory glands</li> </ul>	N <sub>CNS</sub>	<ul style="list-style-type: none"> <li>• Brain</li> <li>• Spinal cord</li> </ul>
	M4	<ul style="list-style-type: none"> <li>• CNS</li> <li>• Heart</li> </ul>		
	M5	<ul style="list-style-type: none"> <li>• CNS</li> <li>• Salivary glands</li> <li>• Iris</li> <li>• Mononuclear blood cells</li> </ul>		

## Cholinergic Stimulants

Direct Acting (Receptor Agonists)	Indirect Acting (Cholinesterase Inhibitors)	
<b>Muscarinic and Nicotinic Agonists</b> <ul style="list-style-type: none"> <li>• Acetylcholine</li> <li>• Carbachol</li> </ul>	<b>Reversible Inhibitors</b> <ul style="list-style-type: none"> <li>• <b>Short Acting</b> <ul style="list-style-type: none"> <li>○ Endrophonium</li> </ul> </li> <li>• <b>Medium Acting</b> <ul style="list-style-type: none"> <li>○ Neostigmine</li> <li>○ Pyridostigmine</li> <li>○ Physostigmine</li> </ul> </li> </ul>	
<b>Muscarinic Agonists</b> <ul style="list-style-type: none"> <li>• Pilocarpine</li> <li>• Bethanecol</li> </ul>	<b>Irreversible Inhibitors</b> <ul style="list-style-type: none"> <li>• Organophosphates                             <ul style="list-style-type: none"> <li>○ Isoflurophate</li> <li>○ Echothiophate</li> </ul> </li> <li>• Soman</li> <li>• Malathion</li> </ul>	
<b>Nicotinic Agonists</b> <ul style="list-style-type: none"> <li>• Nicotine</li> <li>• Suxamethonium Chloride</li> </ul>		
<b>Adverse Effects</b>	<ul style="list-style-type: none"> <li>• Salivation</li> <li>• Diaphoresis</li> <li>• Colic</li> </ul>	<ul style="list-style-type: none"> <li>• GIT hypersensitivity</li> <li>• Headache</li> <li>• Cycloplasm</li> </ul>
<b>Major Contraindications</b>	<ul style="list-style-type: none"> <li>• Asthma                             <ul style="list-style-type: none"> <li>○ Choline ester may induce bronchoconstriction</li> </ul> </li> <li>• Peptic Ulcer                             <ul style="list-style-type: none"> <li>○ Choline ester increases gastric secretion</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Hyperthyroidism                             <ul style="list-style-type: none"> <li>○ Choline ester may induce Atrial Fibrillation in Hyperthyroid patient</li> </ul> </li> <li>• Coronary Vascular Disease                             <ul style="list-style-type: none"> <li>○ Choline ester leads to vasodilation</li> <li>○ May further exacerbate blood flow</li> </ul> </li> </ul>
<b>Signs of Toxicity</b> <b>Antidote = Atropine</b>	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomitting diarrhea</li> <li>• Cutaneous vasodilation</li> <li>• Bronchoconstriction</li> </ul>	<ul style="list-style-type: none"> <li>• Urinary urgency</li> <li>• Salivation</li> <li>• Sweating</li> </ul>

## Pharmacological Effects of Cholinergic Agents

Organs	Effects	Organs	Effects
<b>Eyes</b>	<ul style="list-style-type: none"> <li>• <b>Contract the Spinchter Papilae of the Iris</b> <ul style="list-style-type: none"> <li>○ Leading to Miosis</li> </ul> </li> <li>• <b>Contract the Ciliary muscle</b> <ul style="list-style-type: none"> <li>○ Reduced far vision accomodation leading to Cycloplasm</li> <li>○ Pull the iris away from the Anterior Chamber</li> <li>○ Open the Trabeculae Meshworks</li> </ul> </li> <li>• These 2 will lead to drainage of Aqueous humor away from Anterior Chamber through the Canal of Schlemm                             <ul style="list-style-type: none"> <li>○ <b>Reduce the Intraocular pressure</b></li> </ul> </li> </ul>	<b>Heart</b>	<ul style="list-style-type: none"> <li>• <b>Negative Chronotropic (heart rate)</b> <ul style="list-style-type: none"> <li>○ Mediated by M2 receptors</li> <li>○ Decrease phase 4 Diastolic Depolarization                                     <ul style="list-style-type: none"> <li>▪ Prolong the membrane potential to reach threshold level</li> </ul> </li> </ul> </li> <li>• <b>Negative Dromotropic (conduction velocity)</b> <ul style="list-style-type: none"> <li>○ Excessive vagal tone can lead to massive Bradycardia                                     <ul style="list-style-type: none"> <li>▪ May lead to a partial or total heart block</li> </ul> </li> <li>○ Reduction of Ca<sup>2+</sup> channels opening mediates reduction in heart rate</li> </ul> </li> <li>• <b>Negative Ionotropic (heart contractility)</b> <ul style="list-style-type: none"> <li>○ Prominently affecting Artil rather than Ventricular</li> <li>○ Due to reduction in inward movement of Ca<sup>2+</sup></li> </ul> </li> </ul>
<b>Blood Vessels</b>	<ul style="list-style-type: none"> <li>• <b>Marked vasodilation, due to</b> <ul style="list-style-type: none"> <li>○ Relaxation of smooth muscle cells through endothelial release of                             <ul style="list-style-type: none"> <li>▪ Nitric Oxide</li> <li>▪ Endothelium-derived Relaxing Factor (EDRF)</li> </ul> </li> <li>○ Inhibition of Post-Ganglionic release of Norepinephrine by Ach</li> <li>○ Direct stimulation through Vagus nerve</li> </ul> </li> <li>• <b>Ach may cause vasoconstriction during Endothelial damage</b></li> </ul>	<b>GIT</b>	<ul style="list-style-type: none"> <li>• <b>Intestinal effects</b> <ul style="list-style-type: none"> <li>○ Increase in                             <ul style="list-style-type: none"> <li>▪ Peristalsis</li> <li>▪ Tone</li> <li>▪ Contraction amplitude</li> </ul> </li> <li>○ Mediated by M3</li> <li>○ M2 reduces cAMP formation</li> </ul> </li> <li>• <b>Glandular effects</b> <ul style="list-style-type: none"> <li>○ Strongly stimulate                             <ul style="list-style-type: none"> <li>▪ Salivary glands</li> <li>▪ Gastric glands</li> </ul> </li> <li>○ Lessly stimulate                             <ul style="list-style-type: none"> <li>▪ Pancreatic gland</li> <li>▪ Small intestine gland</li> </ul> </li> </ul> </li> <li>• <b>Relax most spinchters</b></li> </ul>
<b>Genitourinary Tract</b>	<ul style="list-style-type: none"> <li>• <b>Contraction of Detrusor muscle of the Urinary Bladder</b></li> <li>• <b>Relax the Trigone and Bladder Spinchter</b> <ul style="list-style-type: none"> <li>○ Increase maximal voluntary voiding pressure</li> <li>○ Decrease bladder capacity</li> </ul> </li> <li>• <b>Mediated by M2 and M3 receptors</b></li> </ul>	<b>Respiratory</b>	<ul style="list-style-type: none"> <li>• <b>Bronchoconstriction</b></li> <li>• <b>Increase mucus secretion</b> by Tracheobronchial glands</li> </ul>
<b>Miscellaneous</b>	<ul style="list-style-type: none"> <li>• <b>Increase secretion of</b> <ul style="list-style-type: none"> <li>○ Thermoregulatory sweat glands</li> <li>○ Lacrimal gland</li> <li>○ Nasopharyngeal gland</li> </ul> </li> </ul>		

## Parasympathomimetic Agents

### Muscarinic and Nicotinic Agonists

Drugs	Mechanism of Action	Clinical Indications
<b>Acetylcholine</b> <ul style="list-style-type: none"> <li>• Inhalation</li> </ul>	<b>Excitatory Effects</b> <ul style="list-style-type: none"> <li>• M3 receptors                             <ul style="list-style-type: none"> <li>○ Constriction of Sphincter Papillae                                     <ul style="list-style-type: none"> <li>▪ Miosis</li> <li>▪ Reduce intraocular pressure</li> </ul> </li> <li>○ Increase GIT motility and secretion</li> <li>○ Stimulates                                     <ul style="list-style-type: none"> <li>▪ Bronchial glands</li> <li>▪ Salivary glands</li> <li>▪ Sweat glands</li> <li>▪ Lacrimal glands</li> </ul> </li> <li>○ Contract smooth muscle of                                     <ul style="list-style-type: none"> <li>▪ Uterus</li> <li>▪ Bronchioles</li> <li>▪ Ureters</li> <li>▪ Urinary bladder</li> </ul> </li> </ul> </li> </ul> <b>Depressive Effects</b> <ul style="list-style-type: none"> <li>• M2                             <ul style="list-style-type: none"> <li>○ Negative Inotropic</li> <li>○ Negative Chronotropic</li> <li>○ Vasodilation</li> </ul> </li> </ul>	Experimentally due to its short half in respect to its extensive metabolism by <ul style="list-style-type: none"> <li>• Acetylcholinesterase</li> <li>• Plasma Cholinesterase</li> </ul>
<b>Carbachol</b> <ul style="list-style-type: none"> <li>• Eye drops</li> </ul>		<ul style="list-style-type: none"> <li>• Miotic agent</li> </ul>

### Muscarinic Agonists

Drugs	Mechanism of Action	Clinical Indications
<b>Pilocarpine</b> <ul style="list-style-type: none"> <li>• Eye drops</li> </ul>	<ul style="list-style-type: none"> <li>• Miosis</li> <li>• Cycloplasm</li> <li>• Decrease intraocular pressure</li> </ul>	<ul style="list-style-type: none"> <li>• Glaucoma</li> </ul>
<b>Carbachol</b> <ul style="list-style-type: none"> <li>• Tablet</li> <li>• Injection</li> </ul>	<ul style="list-style-type: none"> <li>• Stimulates smooth muscle of GIT</li> <li>• Stimulates Detrusor muscles of Urinary Bladder</li> </ul>	<ul style="list-style-type: none"> <li>• Postoperative Abdominal Distension</li> <li>• Gastric Atony</li> <li>• Gastroparesis</li> <li>• Urinary incontinence</li> <li>• Xerostomia</li> <li>• Sjogren syndrome</li> </ul>
<b>Methacholine Chloride</b> <ul style="list-style-type: none"> <li>• Inhalation</li> </ul>	<ul style="list-style-type: none"> <li>• Synthetic Choline ester</li> <li>• Non-selective Muscarinic agonist</li> </ul>	<ul style="list-style-type: none"> <li>• Bronchial challenge test                             <ul style="list-style-type: none"> <li>○ Use to diagnose bronchial hypersensitivity</li> </ul> </li> <li>Other therapeutic is limited due to extensive                             <ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Hypotension</li> </ul> </li> </ul>