

Effect of direct acting cholinceptor stimulants (nicotinic & muscarinic agonists)

Direct Organ Effect	1. Eye (M3)	<ul style="list-style-type: none"> • Miosis-pupil constriction → thru contraction of circular muscles (sphincter muscles). • near vision focus & aqueous humor outflow into canal of Schlemm → thru contraction of ciliary muscles *used to treat glaucoma *glaucoma: increased intraocular (inside the eye) pressure.
	2. Heart (M2)	<ul style="list-style-type: none"> ↓ rate of SA node (negative chronotropy) ↓ contractile strength of Atria & Ventricles* <small>small decrease</small> (negative inotropy) ↓ conduction velocity (negative dromotropy) & ↑ refractory period in Atrioventricular node
	3. Blood vessels (M3)	Dilation of Arteries & veins via NO(nitric oxide)
	4. Lung (M3)	<ul style="list-style-type: none"> • bronchospasm –contraction of bronchial muscle • ↑ bronchial secretion by stimulating bronchial glands
	5. Gastrointestinal tract (M3)	<ul style="list-style-type: none"> • ↑ motility & secretion Yet, sphincter relaxation
	6. Urinary bladder(M3)	<ul style="list-style-type: none"> • contraction of detrusor. • voiding of urine by relaxation of trigone & sphincter. **Genitourinary tract has (M2 + M3) receptors
	7. glands (M3)	↑ secretion of sweat, salivary, lacrimal, nasopharyngeal
Whole Systemic Effect	1. CVS (M2+ M3—endothelium)	<ul style="list-style-type: none"> • administration of low Ach IV dose → hypotension & reflex ↑HR • administration of high Ach IV dose → hypotension & Bradycardia (↓HR); ↓ SA, ↓ AV ↓ contraction Atria & ventricles. • IV administration of muscarinic agonist causes vasodilation (NO/cGMP pathway) • pilocarpine—a muscarinic agonist; causes vasoconstriction + hypertension. antidote → atropine • nicotine causes tachycardia & hypertension (sympathomimetic/sympathetic effect).
	2. Respiratory	Acute attacks of bronchial asthma due to ↑ bronchoconstriction & bronchial secretions
	3. G.I. (M2 +M3)	<ul style="list-style-type: none"> • muscarinic agonists: ↑ motility (peristaltic activity) + ↑ secretion (salivary glands & gastric glands; ↑ stomach acidity) + relaxed sphincters. • nicotine causes diarrhea, nausea, vomiting by stimulating the parasympathetic ganglia.

	4.CNS	<ul style="list-style-type: none"> • Pilocarpine -muscarinic agonist- can penetrate the blood brain barrier & stimulate M1 receptors in the brain and cause epilepsy (tested on rats) • high levels of nicotine cause tremor, emesis (vomiting), & stimulation of the respiratory center, and even higher levels of nicotine cause convulsion & fatal coma → in this case nicotine stimulates presynaptic nicotinic receptors in CNS that regulate the release of several neurotransmitters. • nicotine increases vagus nerve activity—parasympathetic activity.
	5. Autonomic ganglia	<p>At low concentrations:</p> <ul style="list-style-type: none"> • Nicotine: ↑NE by binding to nicotinic receptors of the sympathetic ganglia. ↑Ach by binding to nicotinic receptors of the parasympathetic ganglia. <p>At high concentrations: nicotine causes ganglia blockade (depolarizing blockade)</p> <ul style="list-style-type: none"> • stimulating the autonomic ganglia both sympathetic and parasympathetic has a wide systemic effect.
	6.neuromuscular junction (NMJ) in skeletal muscles	<ul style="list-style-type: none"> • nicotine produces various contractile responses in skeletal muscles (ranges from disorganized fasciculations—strong contractions). • at high conc. causes depolarization blockade → flaccid paralysis of skeletal muscles.

Extra side notes:

- chronotropy: changing HR by changing SA rhythm
negative chronotropic effect **decreases** HR
- inotropy: changing muscle contraction.
negative inotropy causes ↓force of contraction of the heart.
- dromotropy: changing conduction speed of AV node.
- ventricles have a small number of muscarinic receptors that's why they're slightly affected with a small decrease in contractile strength.
- detrusor: smooth muscle found in the wall of the bladder.
- uterus isn't sensitive to muscarinic agonists unlike the genitourinary tract.
- the brain is rich in muscarinic receptors whereas the spinal cord is rich in nicotinic receptors.
- because nicotine causes tachycardia it elevates BP which stimulates baroreceptors in CNS and stimulates vagal discharge (parasympathetic neuron) causing reflex bradycardia.

Systemic Effects of cholinesterase inhibitors

CNS	<p>Organophosphates & physostigmine can only penetrate the BBB:</p> <ul style="list-style-type: none"> • cause subjective alerting response at low conc. • generalized convulsion maybe followed by coma & respiratory arrest at high conc.
CVS	<ul style="list-style-type: none"> • modest bradycardia: negative inotropic, dromotropic & chronotropic effects. • fall in cardiac output. • no direct actions on vascular smooth muscles. • rise in BP; due to increase in vascular resistance as a result of stimulating the sympathetic ganglion.
NMJ	<p>At low concentrations:</p> <ul style="list-style-type: none"> • ↑ strength of muscles contraction by Intensifying & prolonging the action of Ach. <p>At high concentrations:</p> <ul style="list-style-type: none"> • fibrillation • Antidromic firing • fasciculations—irregular, incoordinate contraction of muscle fibers <p>*quaternary carbamate cholinesterase inhibitors have direct nicotinic agonist effect in NMJ, which makes them effective therapeutic agents for treating myasthenia gravis.</p>
Eye, respiratory tract, GIT, urinary tract	<p>Similar effects of direct-acting cholinomimetics; Increased GI function, salivation, lacrimation, urination, diarrhea, urination</p>

CNS = central nervous system

CVS = cardiovascular system

NMJ = neuromuscular junction

GIT = gastrointestinal tract

BBB: blood brain barrier

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