Autonomic pharmacology

Cholinergic pharmacology

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- **Sources**
- **Lippincott Illustrated Reviews: Pharmacology 7th Edition**
- **Katzung ; Basic & Clinical Pharmacology 14th Edition**
- **Bennett & Brown ; Clinical pharmacology 11th edition**
- **Essentials of Medical Pharmacology; Lafi 09**

Cholinergic pharmacology

ANS – Parasympathetic & Sympathetic Basics

- **Parasympathetic** – "CHOLinergic"
  - Craniosacral, cGMP
    - **MUSCARINIC** - Most
    - **NICOTINIC**: Located at NMJ and Ganglia

Cholinergic Agents

- Also called cholinomimetics , cholinergic stimulants, cholinergic agonists
- Drugs that stimulate the parasympathetic nervous system (PSNS)
- Mimic the effects of the PSNS neurotransmitter
- Acetylcholine (ACh)

Cholinergic Receptors

Two types, determined by:

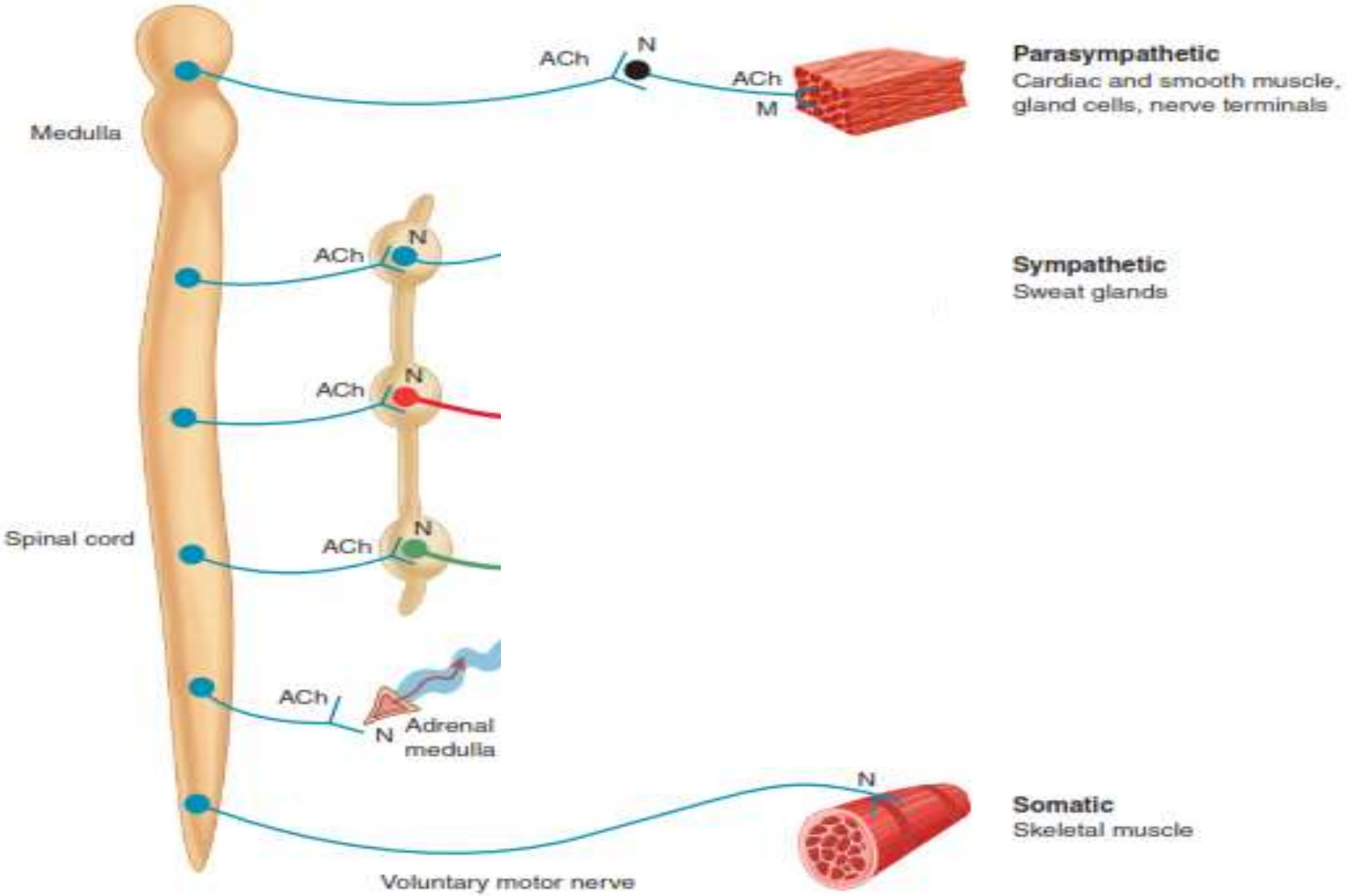
- Location
- Action once stimulated

Nicotinic receptors and Muscarinic receptors

Nicotinic Receptors

- Located in the ganglia of both the PSNS and SNS
- At the skeletal muscle NMJ
- Named “nicotinic” because can be stimulated by the alkaloid nicotine

Nicotinic receptors distribution and effects

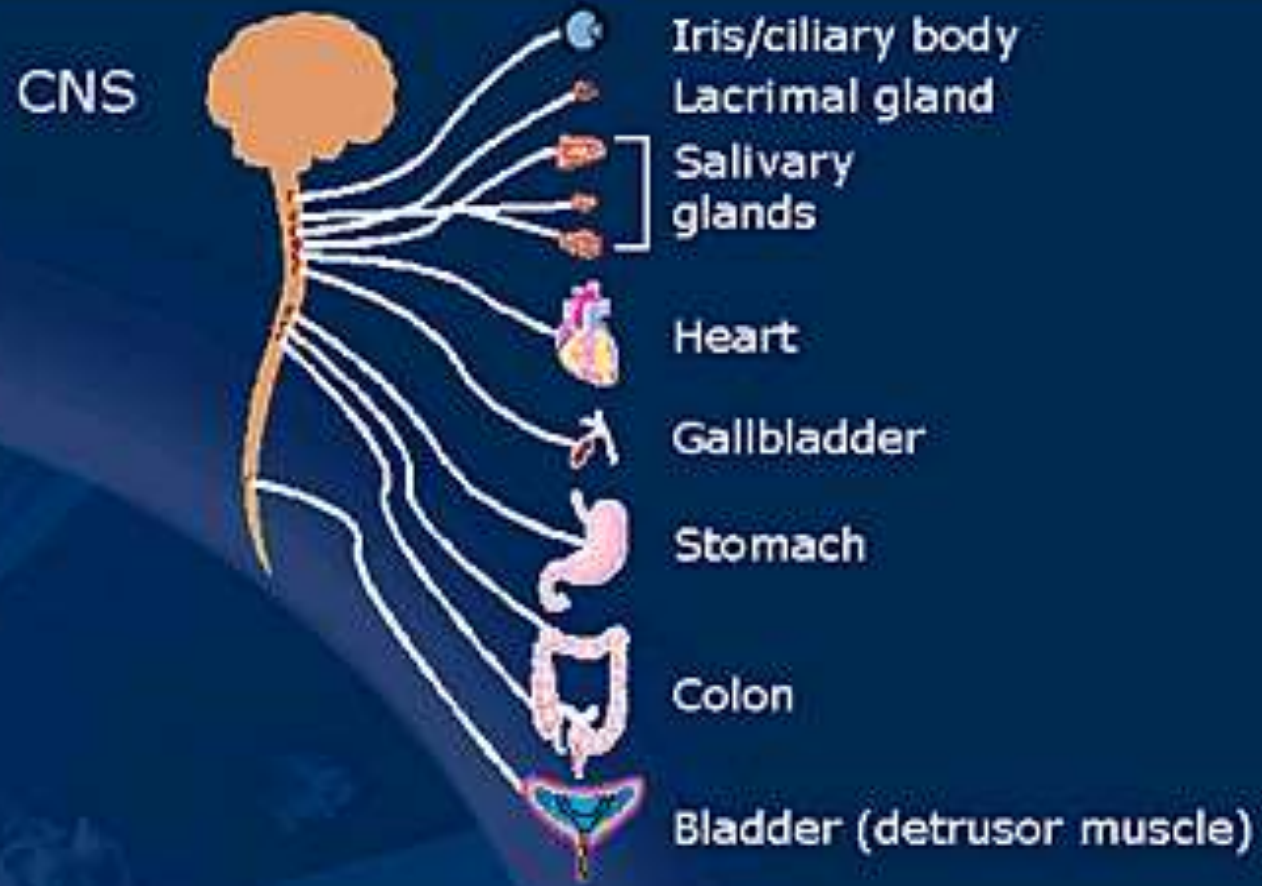


Receptor subtype	Location	Response to receptor activation
Nicotinic$_N$	**All autonomic nervous system ganglia & adrenal medulla**	Stimulation of sympathetic and parasympathetic postganglionic nerves & release of adrenaline from adrenal medulla
Nicotinic$_M$	**Neuromuscular junction**	Contraction of skeletal muscle

Muscarinic Receptors

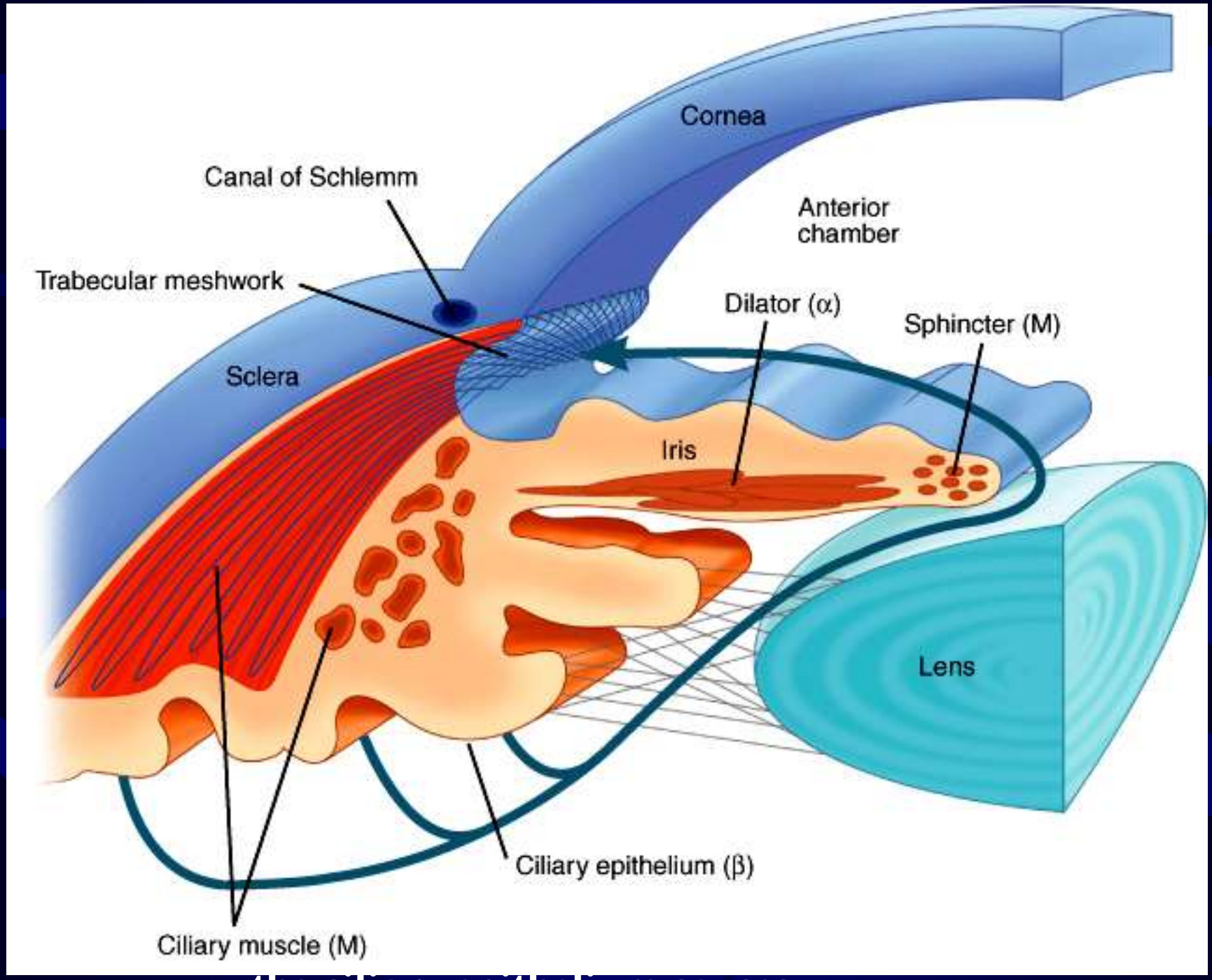
- Located postsynaptically:
  - –Smooth muscle
    - – Cardiac muscle
    - – Glands of parasympathetic fibers
    - – Effector organs of cholinergic sympathetic fibers (Sweat gland)
- Named “muscarinic” because can be stimulated by the alkaloid muscarine

Muscarinic Receptor Distribution



Andersson K-E. *Eur Urol*. 2002;1(Suppl):23-28.

Muscarinic	**All parasympathetic target organ & Sweat glands**	
	Eye	Contraction of the ciliary muscle focuses for near vision
		Contraction of the iris sphincter causes miosis (decreased pupil diameter)



the ciliary epithelium causes

Cholinergic Receptor

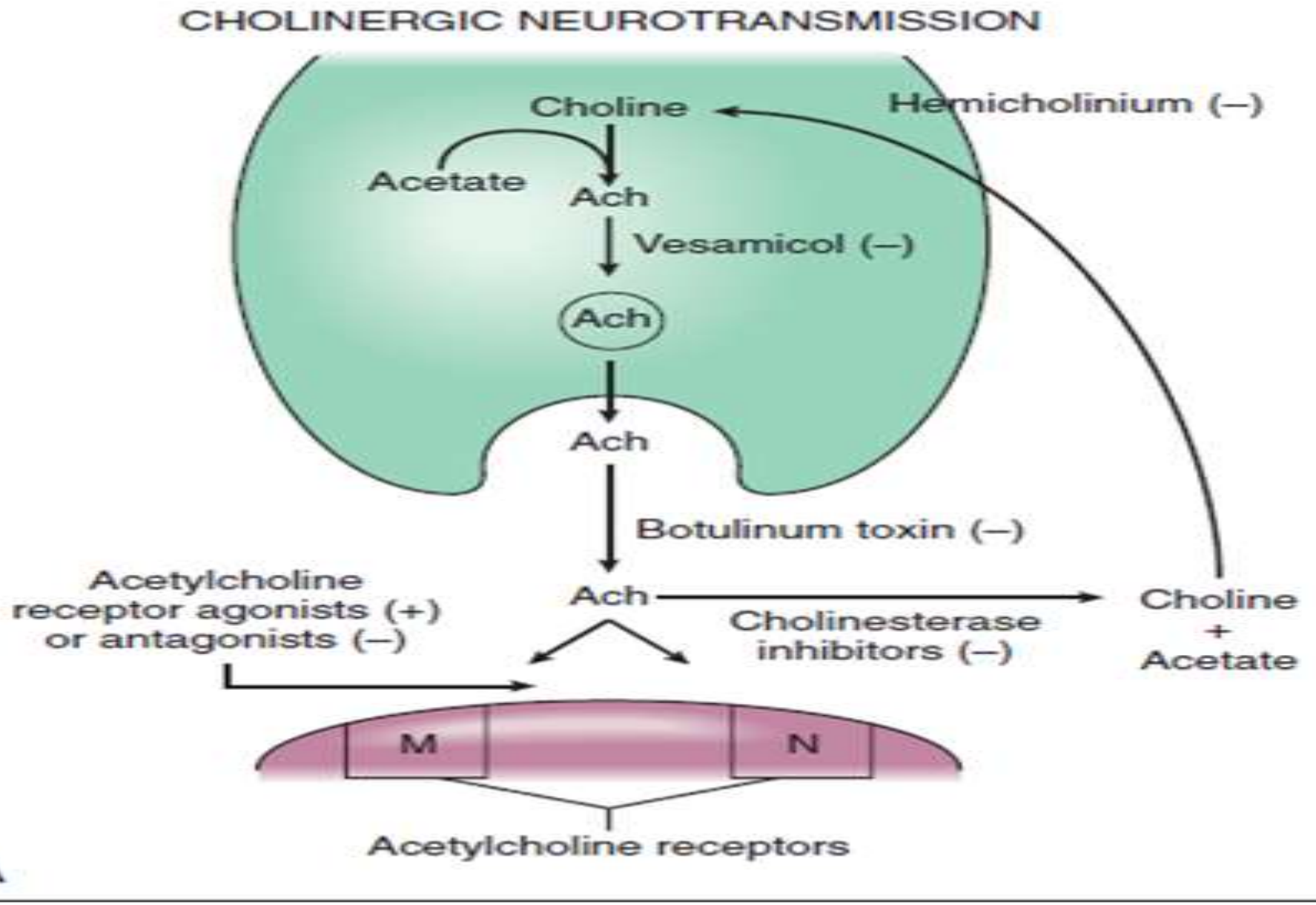
Receptor subtype	Location	Response to receptor activation
Muscarinic	**Heart**	Decreased rate (Vagal)
	Lung	Contraction of bronchi Promotion of secretion
	Bladder	Voiding (Contraction)
	GIT	Salivation (secretion) Increased gastric secretion Defecation (Contraction)

Receptor subtype	Location	Response to receptor activation
Muscarinic	**Sweat gland**	Generalized sweating
	Sex organs	Erection
	Blood vessels ** **Endothelium**	Vasodilatation

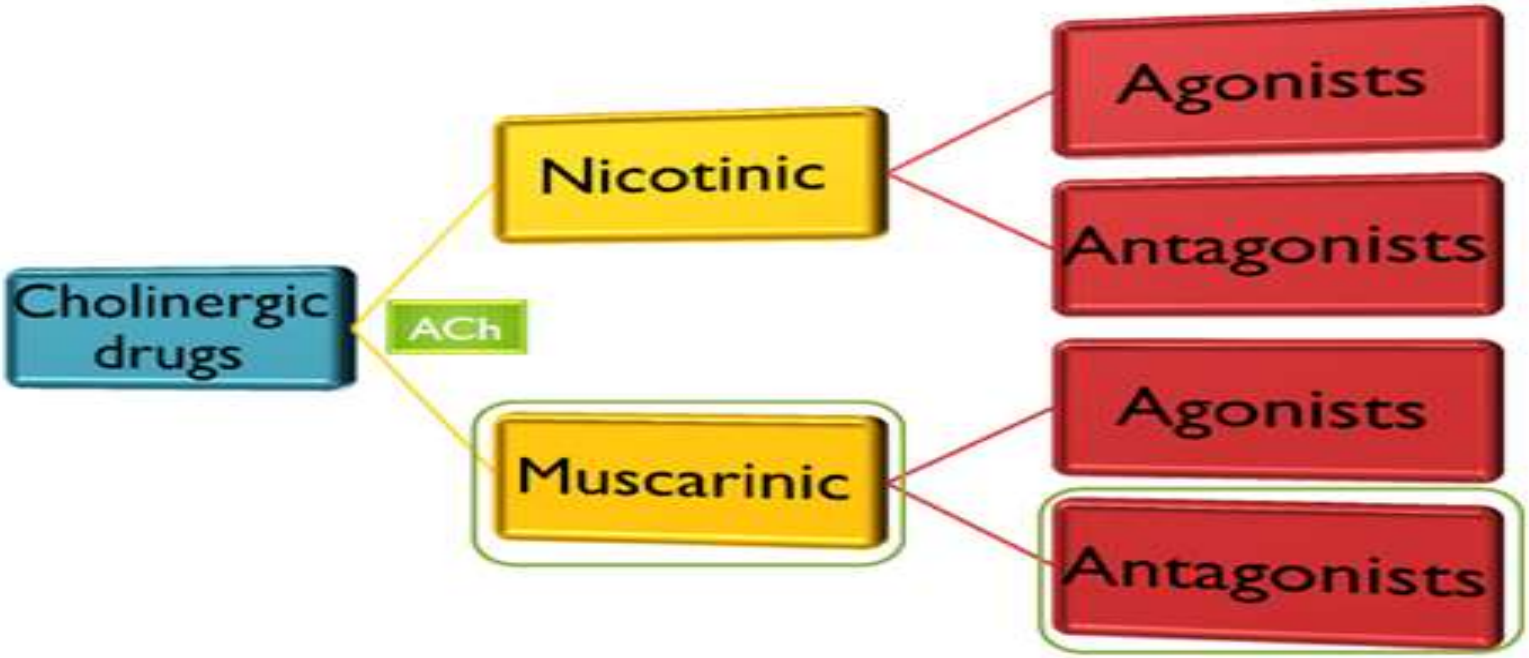
Parasympathetic System

- Cholinergic

- **M1** – CNS/ENS
- **M2** – Heart
- **M3** – **EG MP AC BB**
  - Increases **E**xocrine Gland Secretion
  - Increases **G**ut Motility
  - **M**iosis via **P**upillary sphincter
  - **A**ccommodation via **C**iliary
  - **B**ronchoconstriction
  - **B**ladder constriction


CHOLINERGIC NEUROTRANSMISSION
Choline
Hemicholinium (–)
Acetate
Ach
Vesamicol (–)
Ach
Ach
Botulinum toxin (–)
Acetylcholine receptor agonists (+) or antagonists (–)
Ach
Cholinesterase inhibitors (–)
Choline + Acetate
M
N
Acetylcholine receptors
A

Cholinergics



Drug Effects of Cholinergic Agents

- Effects seen when the PSNS is stimulated.
- The PSNS is the “rest and digest” system.

Drug Effects of Cholinergic Agents

- Stimulate intestine and bladder
  - Increased gastric secretions
  - Increased gastrointestinal motility
  - Increased urinary frequency
- Stimulate pupil
  - Constriction (miosis)
  - Reduced intraocular pressure
- Increased salivation and sweating

Drug Effects of Cholinergic Agents

- Cardiovascular effects
  - Decreased heart rate
  - Vasodilation
- Respiratory effects
  - Bronchial constriction, narrowed airways

Drug Effects of Cholinergic Agents

- At recommended doses, the cholinergics primarily affect the MUSCARINIC receptors.
- At high doses, cholinergics stimulate the NICOTINIC receptors.

Cholinergic Agents: Therapeutic Uses

Direct-Acting Agents

- Reduce intraocular pressure
- Useful for glaucoma and intraocular surgery

  Examples:

  - acetylcholine,
  - carbachol,
  - pilocarpine

  -Topical application due to poor oral absorption

Cholinergic Agents: Therapeutic Uses

Direct-Acting Agent—Bethanechol

- Increases tone and motility of bladder and GI tract
- Relaxes sphincters in bladder and GI tract, allowing them to empty
- Helpful for postsurgical atony of the bladder and GI tract

Cholinergic Agents: Therapeutic Uses

Indirect-Acting Agents : ACH Esterase Inhibitors

- Cause skeletal muscle contractions
- Used for diagnosis and treatment of myasthenia gravis
- Used to reverse neuromuscular blocking agents
- Used to reverse anticholinergic poisoning (antidote)

Examples:

- physostigmine,
- pyridostigmine

Cholinergic Agents: Therapeutic Uses

Indirect-Acting Agent—donepezil (Aricept)

- Used in the treatment of mild to moderate Alzheimer's disease.
- Helps to increase or maintain memory and learning capabilities.

Cholinergic Agents: Side Effects

Side effects are a result of overstimulation of the PSNS.

- Cardiovascular:
  - Bradycardia, hypotension, conduction abnormalities (AV block and cardiac arrest)
- CNS:
  - Headache, dizziness, convulsions
- Gastrointestinal:
  - Abdominal cramps, increased secretions, nausea, vomiting

Cholinergic Agents: Side Effects

- Respiratory:
  - Increased bronchial secretions, bronchospasms
- Other:
  - Lacrimation, sweating, salivation, loss of binocular accommodation, miosis

Cholinergic Agents: Interactions

- Anticholinergics, antihistamines, sympathomimetics
- Antagonize cholinergic agents, resulting in decreased responses

Effects of Cholinergic Agent Excess or toxicity as in gas war

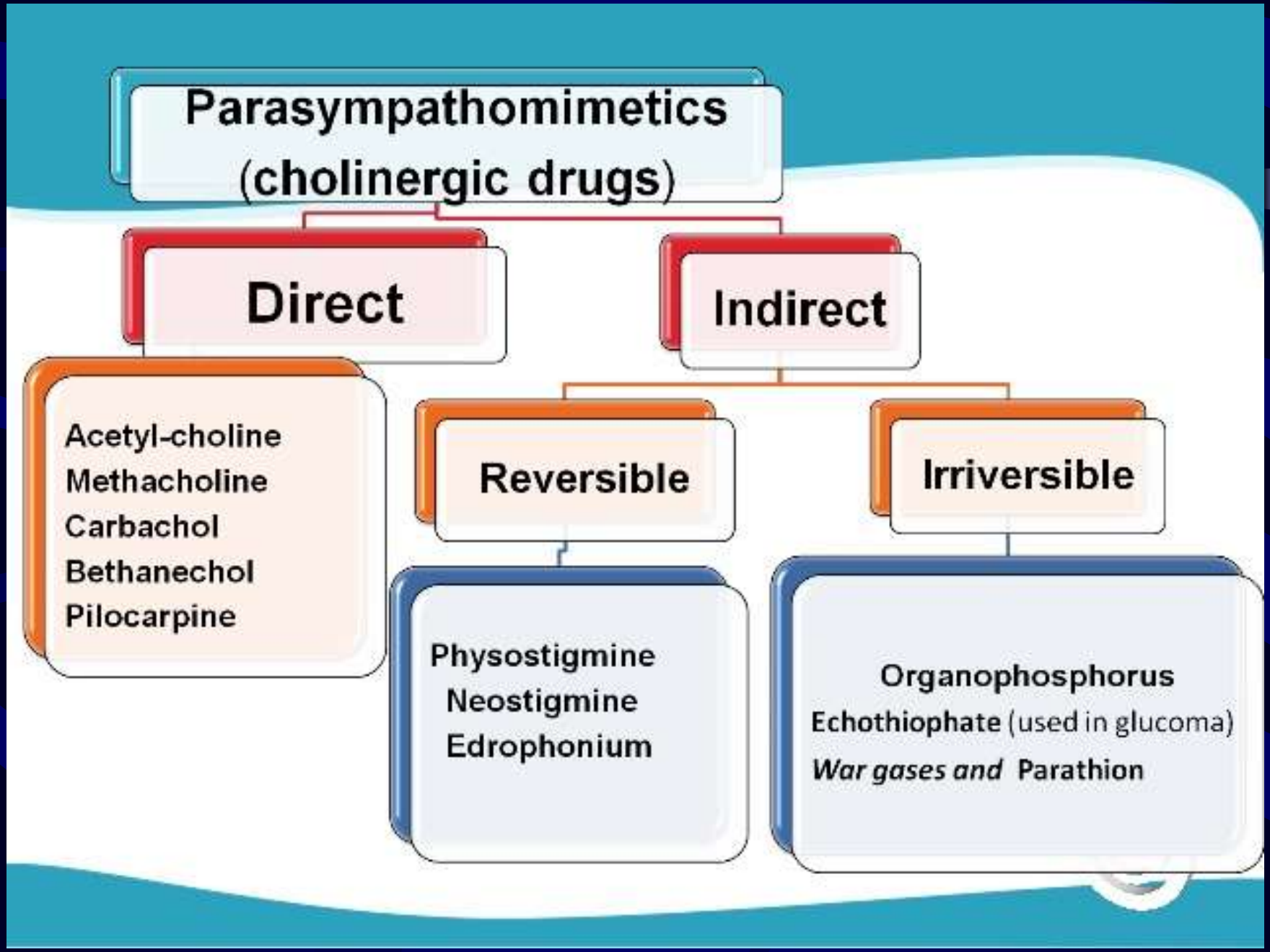
"SLUDGE"

- *S*alivation
- *L*acrimation
- *U*rinary incontinence
- *D*iarrhea
- *G*astrointestinal cramps
- *E*mesis

Toxicity of Acetylcholinesterase Inhibitors

DUMBELSS

- Diarrhea
- Urination
- Miosis
- Bronchoconstriction
- Excitation (muscle and CNS)
- Lacrimation
- Salivation
- Sweating


Parasympathomimetics
(cholinergic drugs)
Direct
Indirect
Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine
Reversible
Irriversible
Physostigmine
Neostigmine
Edrophonium
Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

Cholinergic Agents: Mechanism of Action

- Direct-acting (agonist)
  - Bind to cholinergic receptors, causing stimulation
  - Acts on the receptor sites to activate a tissue response

Drug	Action	Selected therapeutic uses and important remarks
Directly Acting Agents **Ach like**		
Bethane**chol**	**Muscarinic receptors (activation)**	Atonic bladder (in postpartum or postoperative non-obstructive urinary retention generalised cholinergic stimulation*
Pilocarpine	**Muscarinic receptors (activation)**	Narrow (closed) and wide (open) angle glaucoma; enter the brain - CNS-disturbances
Carba**chol**	**Muscarinic & nicotinic N_N-receptors (activation)**	glaucoma, when used topically shows little or no adverse-effects Rarely used (high potency and long duration)

* Generalised cholinergic stimulation: salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhoea, and bronchospasm; if the drug enters the CNS (e.g. physostigmine), it would show CNS disturbances which may lead to convulsion.

CHOLinergics

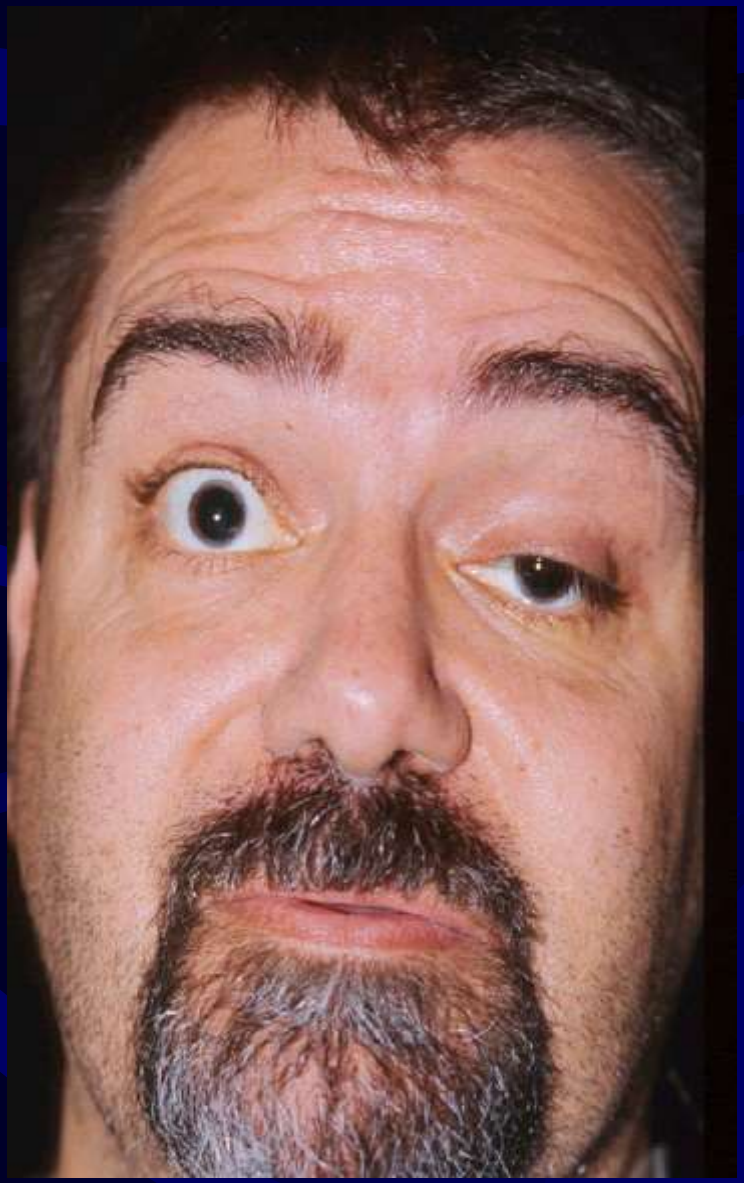
- **BethanaCHOL** – Post op and neurogenic ileus and urinary retention
- **CarbeCHOL** – Glaucoma, pupillary contraction, and relief of IOP, also for Post op urinary retention
- **MethaCHOLine** – Induces bronchospasm used in Asthma Challenge Test
- **Pilocarpine** –Cystic Fibrosis Sweat Test; "PiloCHOLpine"

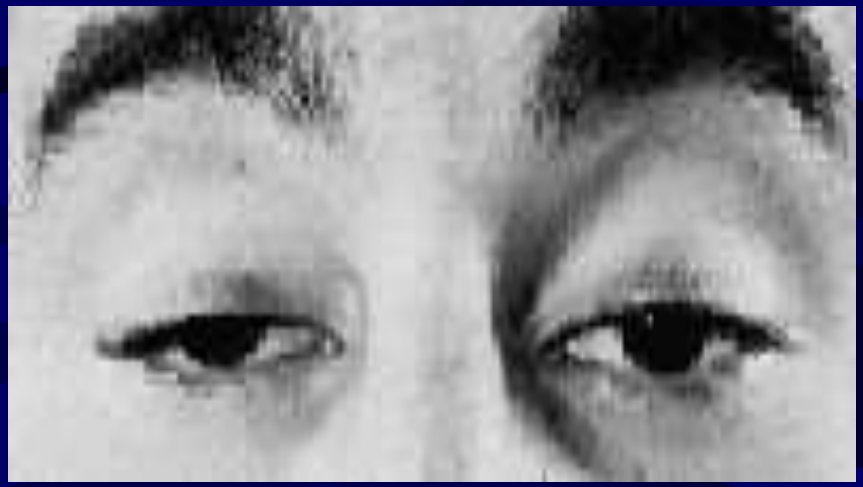
Cholinergic Agents: Mechanism of Action

- Indirect-acting
  - Inhibit the enzyme cholinesterase (chE) (acetylcholinesterase)
  - Cholinesterase- destroys acetylcholine before it reaches the receptor or after it has attached to the receptor site
  - Result: more ACh is available at the receptors

Indirect-Acting Cholinergic Agents (Cholinesterase Inhibitors)

- Reversible
  - Bind to cholinesterase for a period of minutes to hours





Clinically Important Acetylcholinesterase Inhibitors

Edrophonium (Tensilon®)

- Diagnosis of myasthenia gravis ("Tensilon test")

Physostigmine

- Treatment of glaucoma

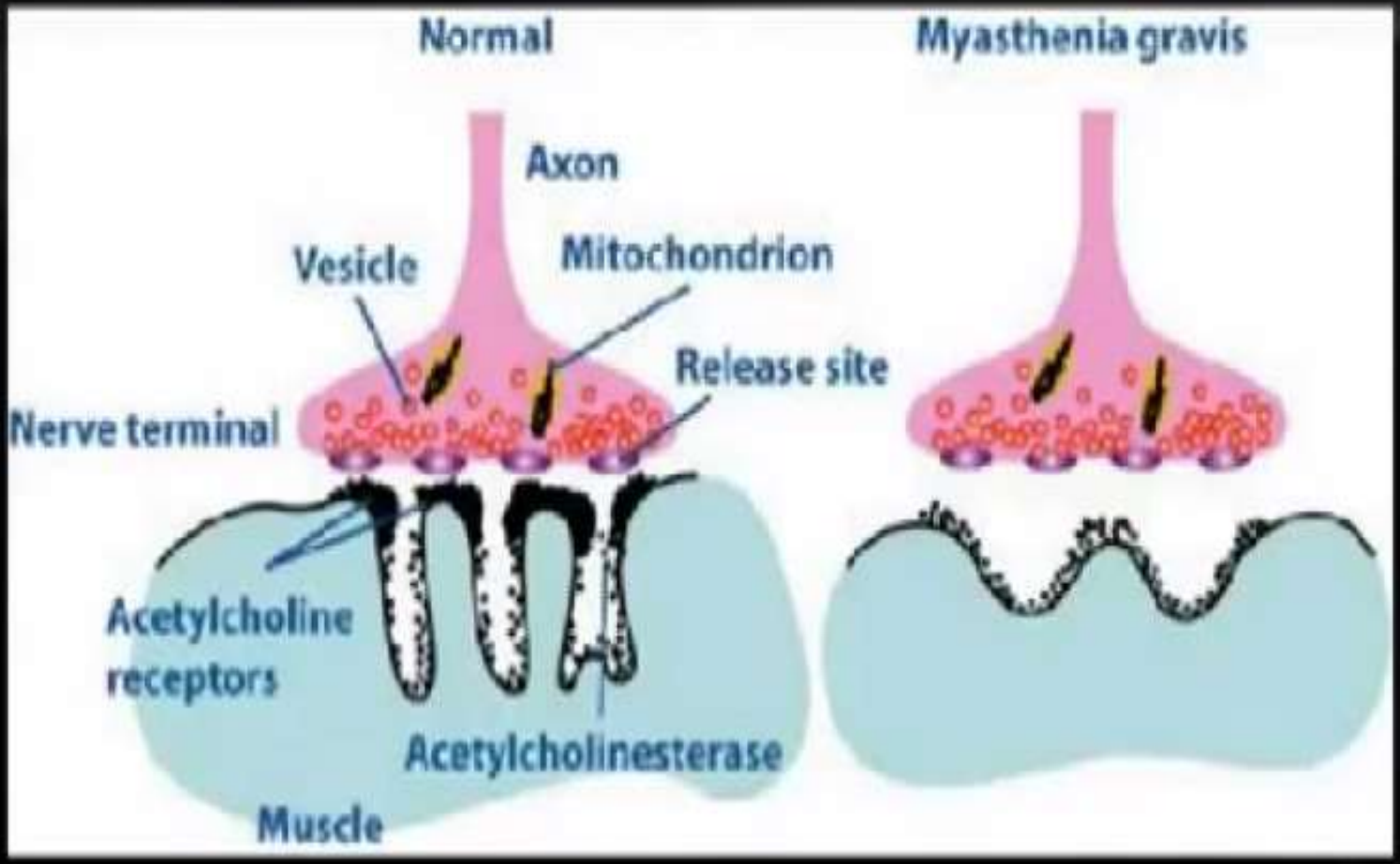
Neostigmine

- Reversal of non-depolarizing neuromuscular blockers
- Treatment of myasthenia gravis

Pyridostigmine

- Treatment of myasthenia gravis

Neuromuscular Junction in Myasthenia Gravis



Drug	Action	Selected therapeutic uses and important remarks
Indirectly Acting (Reversible) Agents Inhibits AChE		
Physostigmine Atropine& TCA antidote		• Atony of bladder and intestine, • **glaucoma,** • overdose with anticholinergics (e.g. atropine, phenothiazines and TCA) **enters - brain**, **-generalised cholinergic stimulation***; (0.5-2 hr)
Demecarium		• **Glaucoma**; (4-6 hr) *CDPPIE
2- Neostigmine		• Atony of bladder and intestine, • overdose with competitive neuromuscular blocking agents (e.g. tubocurarine), • **myasthenia gravis** poorly CNS , generalised cholinergic stimulation ; (0.5-2 hr)
3- Pyridostigmine		• chronic management of myasthenia gravis; (3-6 hr)
4-Ambenonium		• chronic management of myasthenia gravis; (4-8 hr)
1-Edrophonium		• diagnosis of myasthenia gravis, * ENPA • postoperative paralytic ileus

Anti-ACh-Esterases

MOA:

Prevent degradation of ACh increasing endogenous AcH
- More ACh (acetylCHOLine) so more CHOLinergic!

- **Edrophonium** – Dx Myasthenia Gravis, used to differentiate it from cholinergic crisis
- **NeoSTIGmine/PyridoSTIGmine** – Rx Myasthenia Gravis (No BBB)
  - Rx – Myasthenia Gravis, Ileus, Urinary Retention, Reversal of NMJ Blockage
- **PhysoSTIGmine** – Rx for Atropine Overdose (Will cross BBB), also for glaucoma
- **Ecothiophate** – For Glaucoma
- **Donepezil** – For Alzheimer's disease - Lipid Soluble
- **Tacrine** – Lipid Soluble – Rx – Alzheimers

Indirect-Acting Cholinergic Agents (Cholinesterase Inhibitors)

- Irreversible
  - Bind to cholinesterase and form a permanent covalent bond
  - The body must make new cholinesterase

Examples of Organophosphate AChE Inhibitors

Pesticides

Malathion-based insect spray

Nerve gas (VX)

Organophosphates

- Treatment of glaucoma (ecothiopate)
- Insecticides (parathion, malathion)
- Nerve gas (sarin, tabun, VX)

Drug	Action	Selected therapeutic uses and important remarks
Indirectly Acting (Irreversible) Agents (organophosphate, Nerve agent) Covalently binds to AChE (click)		
Isoflurophate (DFP)		chronic management of **open angle glaucoma** (ointment, last for 1 week); enters CNS, generalised cholinergic stimulation* (largely reversed by high dose of atropine); DFP ages in 6-8 hr
Echothiophate		In chronic management of **open angle glaucoma**; (100 hr)

Drug	Action	Selected therapeutic uses and important remarks
Reactivation of Acetylcholinesterase (AChE)		
Pralidoxime 2pam Atropine,	**Displaces organophosphate** **regenerating the enzyme**	Poisoning with organophosphophorus compounds (before enzyme ageing occurs, i.e. loss of an alkyl group from the phosphorylated enzyme); can reverse the effect of DFP except for those in CNS; less effective with **newer nerve agents** (enzyme ageing in seconds).

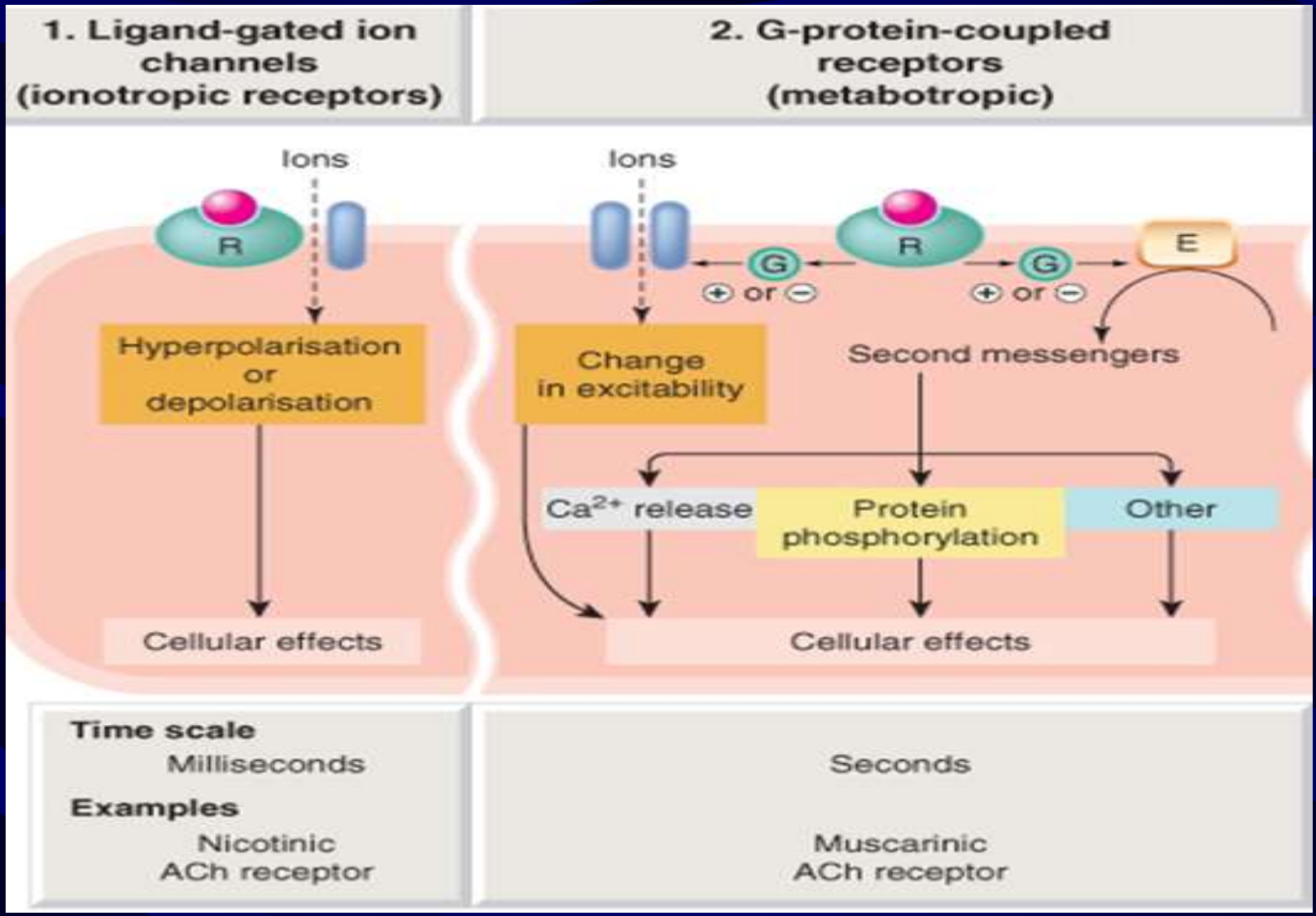

The End

Home work

Summarize in a table

1- Transmitter, receptors, primary locations, postreceptor mechanism, stimulant substances and blockers in the autonomic nervous system.

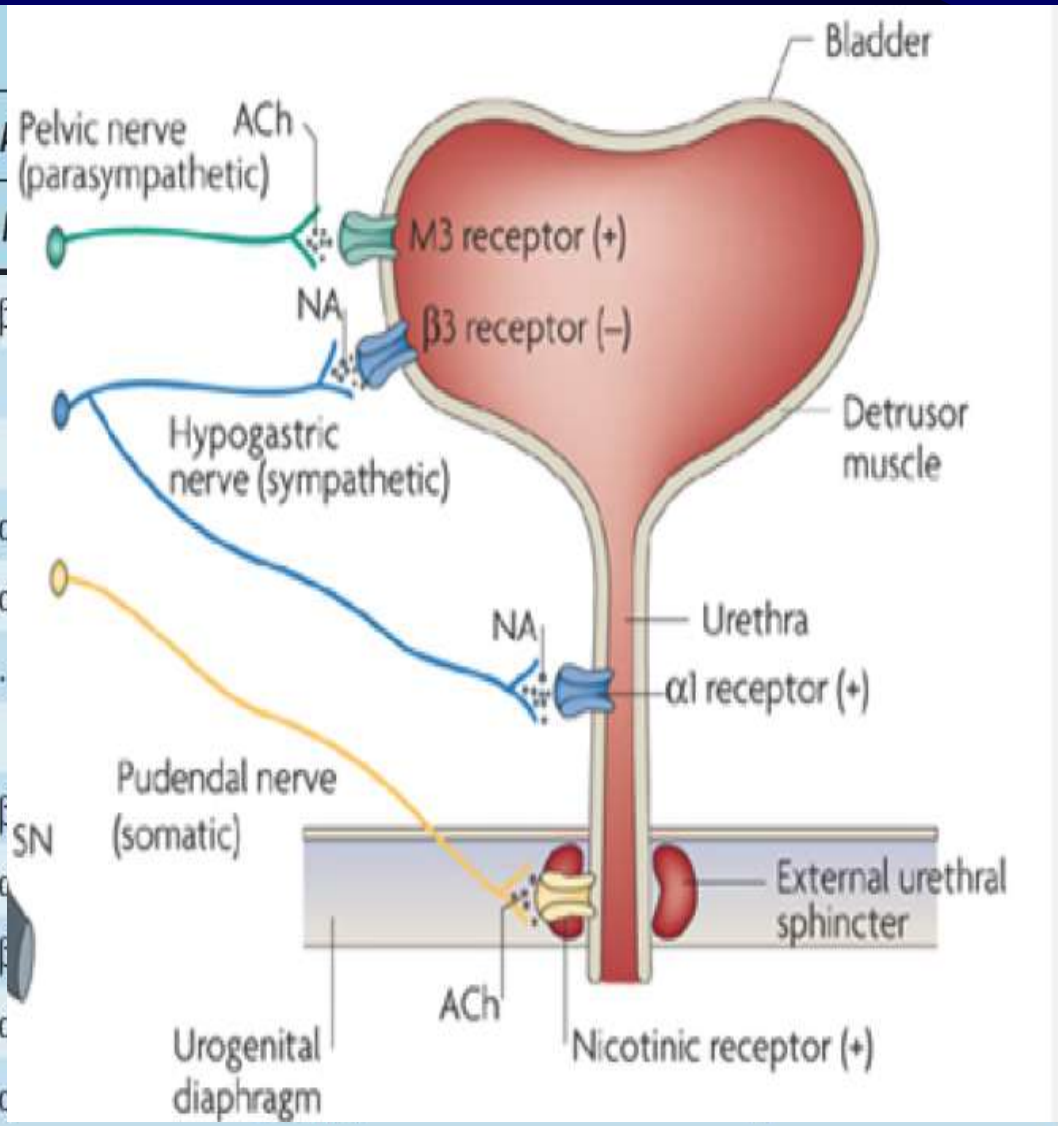
2- Responses of some effector organs to autonomic nerve impulses, and circulating catecholamines and autonomic drugs.


1. Ligand-gated ion channels (ionotropic receptors)
2. G-protein-coupled receptors (metabotropic)
Ions
R
Hyperpolarisation or depolarisation
Cellular effects
Ions
G
R
G
E
⊕ or ⊖
⊕ or ⊖
Change in excitability
Second messengers
Ca2+ release
Protein phosphorylation
Other
Cellular effects
Time scale
Milliseconds
Seconds
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals; receptors typically contain two $\alpha 3$ and one $\beta 4$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular end plates; receptors typically contain two $\alpha 1$ and $\beta 1$ type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization

Organ	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
	Action[1]	*Receptor*[2]	*Action*	*Receptor*[2]
Eye				
Iris radial muscle	Contracts	α_1	…	…
Iris circular muscle	…	…	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	…	…
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	…	…
Skeletal muscle vessels	Relaxes	β_2	…	…
	[Contracts]	α	…	…
	Relaxes[3]	M_3	…	…
Endothelium of vessels in heart, brain, viscera	…	…	Synthesizes and releases EDRF[4]	M_3, M_5[5]

Organ	Sympathetic A Action[1]	
Bronchiolar smooth muscle	Relaxes	
Gastrointestinal tract		
Smooth muscle		
Walls	Relaxes	
Sphincters	Contracts	
Secretion	…	
Genitourinary smooth muscle		
Bladder wall	Relaxes	
Sphincter	Contracts	
Uterus, pregnant	Relaxes	
	Contracts	
Penis, seminal vesicles	Ejaculation	



Organ	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
	Action[1]	*Receptor*[2]	*Action*	*Receptor*[2]
Skin				
Pilomotor smooth muscle	Contracts	α	…	…
Sweat glands				
Eccrine	Increases	M		
Apocrine (stress)	Increases	α		
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	…	…
Liver	Glycogenolysis	β_2, α	…	…
Fat cells	Lipolysis	β_3	…	…
Kidney	Renin release	β_1	…	…

Eccrine sweat glands	**Abundant sweat glands with odorless secretion**	**Lower body temperature**
Apocrine sweat glands	**Less numerous sweat glands with secretions that develop odors**	**Wet skin during pain, fear, emotional upset, and sexual arousal**


The End