Autonomic Nervous System
ANS

Tikrit University

College of Pharmacy

Department of Pharmacology and Toxicology

Ass. Lec. Rabei Abdullah Salih

The Autonomic Nervous System

The autonomic nervous system (ANS), along with the endocrine system, **coordinates the regulation and integration of bodily functions.**

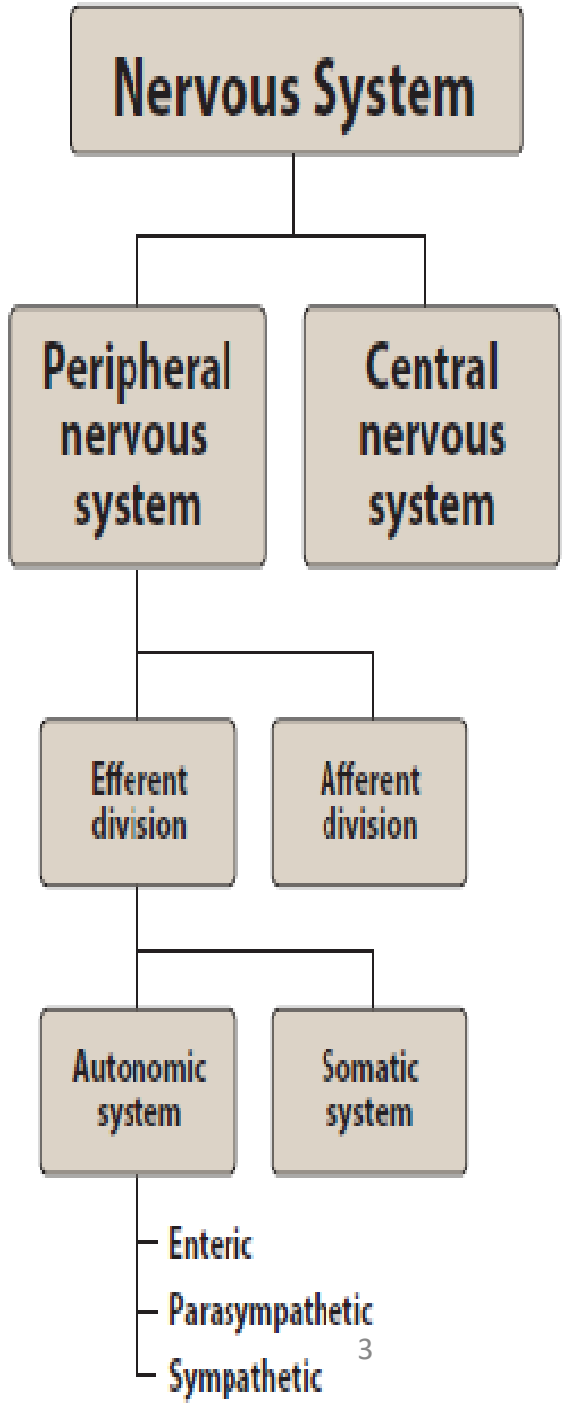
The endocrine system **sends signals** to target tissues by varying the levels of blood-borne hormones.
In contrast, the nervous system exerts its influence by the **rapid transmission of electrical impulses over nerve fibers** that terminate at effector cells, which specifically respond to the release of neuromediator substances.
Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called **autonomic drugs**. These autonomic agents act either by **stimulating** portions of the ANS or by **blocking** the action of the autonomic nerves.

The nervous system is divided into **two** anatomical divisions: the central nervous system (CNS), which is composed of the **brain and spinal cord**, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord that is, any nerves that enter or leave the CNS.

The peripheral nervous system is **subdivided** into the efferent and afferent divisions.

The efferent neurons **carry signals away** from the brain and spinal cord to the **peripheral tissues**, and the afferent neurons **bring information** from the periphery to the CNS.

Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.



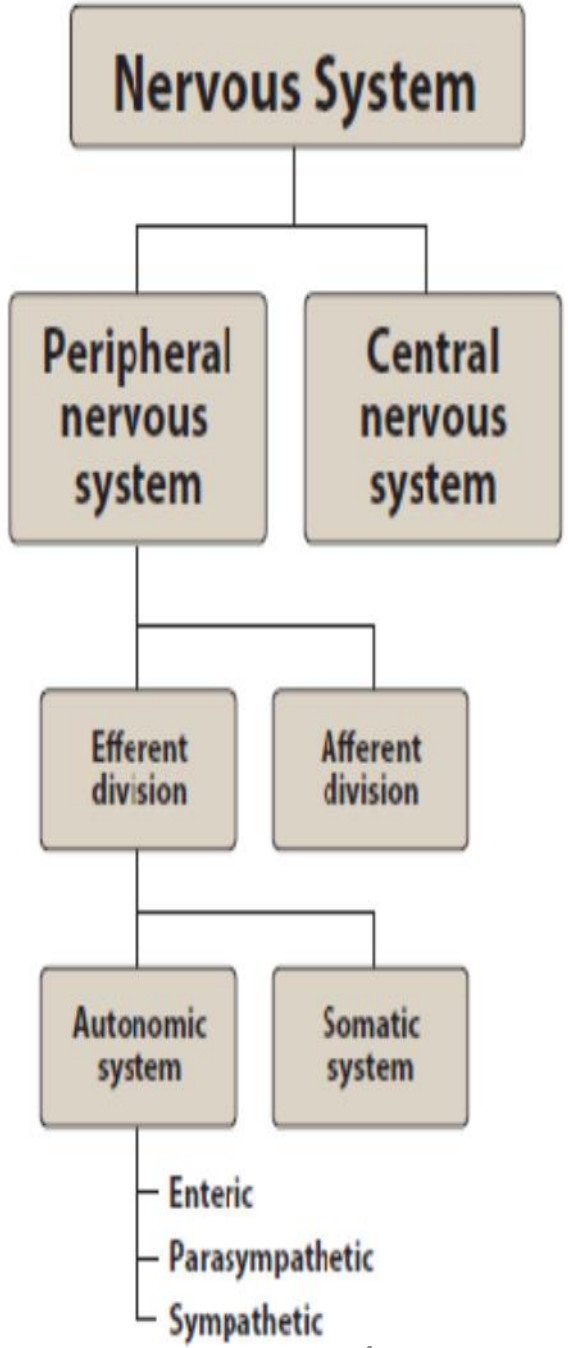
Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: the somatic and the ANS.

The somatic efferent neurons are involved in the **voluntary control of functions such as contraction of the skeletal muscles essential for locomotion.**

The ANS, conversely, regulates the everyday requirements of vital bodily functions **without** the conscious participation of the mind.

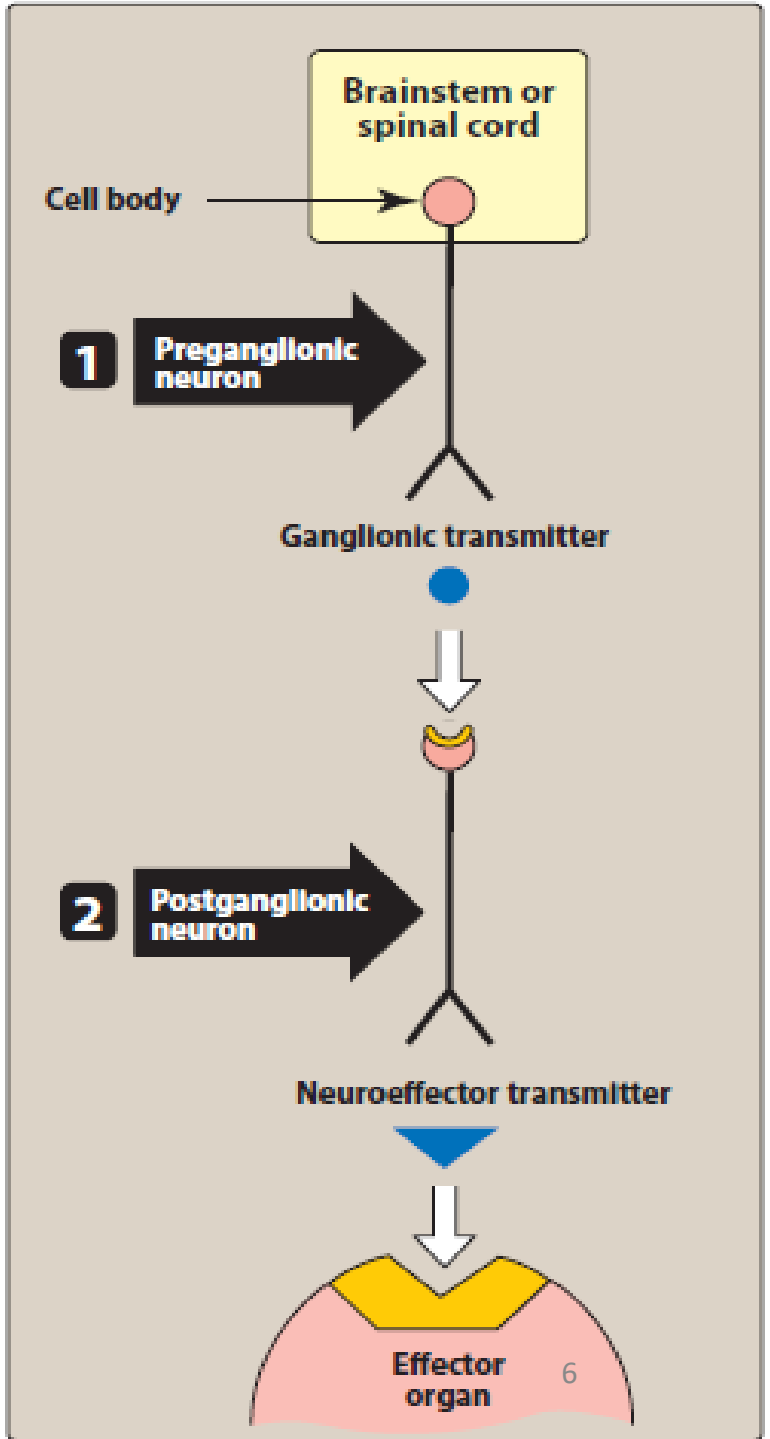
Because of the involuntary nature of the ANS as well as its functions, it is also known as the **visceral, vegetative, or involuntary nervous system.**



It is **composed** of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling **digestion, cardiac output, blood flow, and glandular secretions.**

Anatomy of the ANS

1. Efferent neurons: The ANS carries nerve impulses from the CNS to the effector organs through two types of efferent neurons: the **preganglionic** neurons and the **postganglionic** neuron.
The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. The preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in **ganglia (an aggregation of nerve cell bodies** located in the peripheral nervous system).
The ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as **visceral smooth muscle, cardiac muscle, and the exocrine glands.**

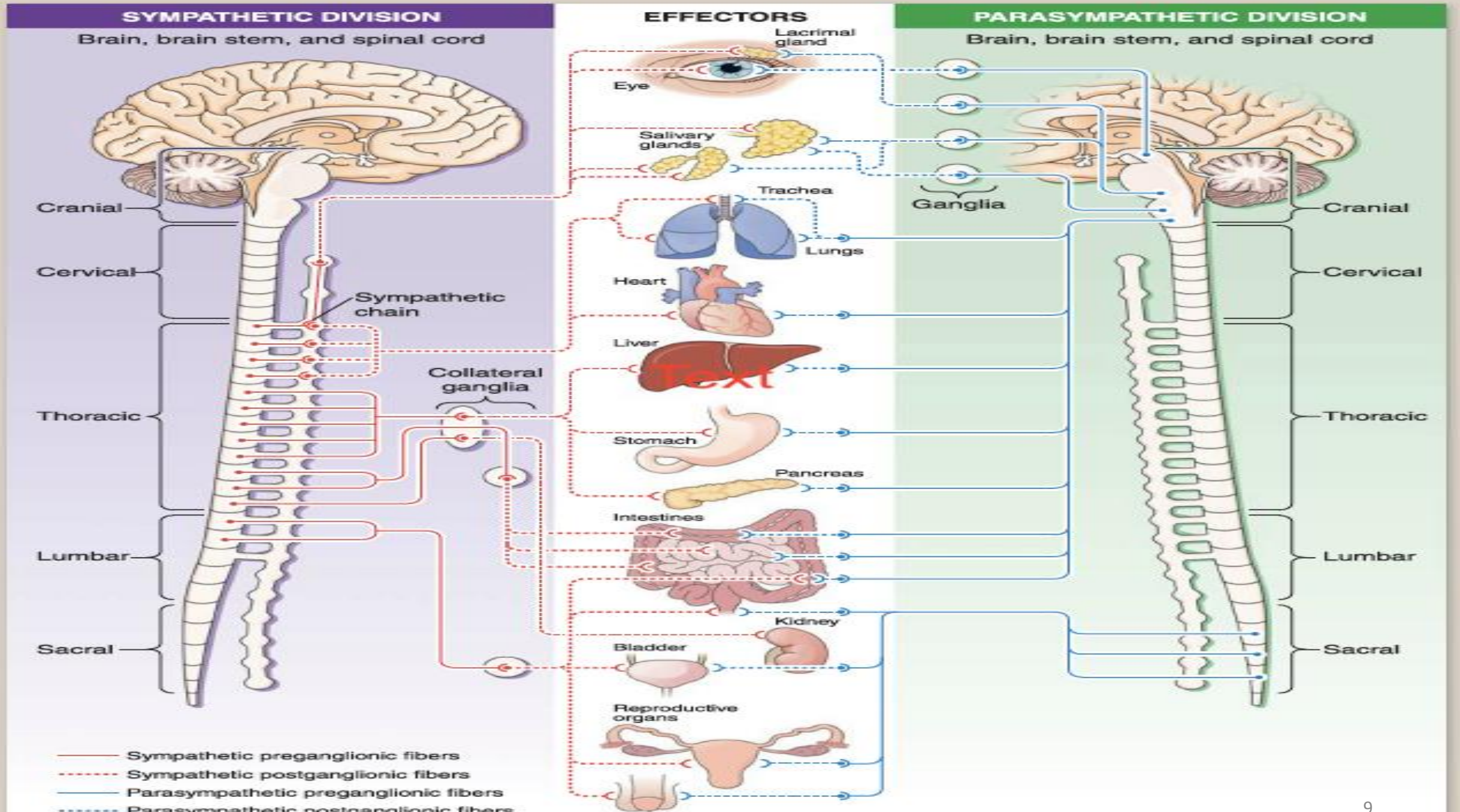


2. Afferent neurons:

The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and in signaling the CNS to influence the efferent branch of the system to respond.

3. Sympathetic neurons:

The efferent ANS is **divided** into the **sympathetic and the parasympathetic** nervous systems, as well as the enteric nervous system.
Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions. The **preganglionic** neurons of the sympathetic system come from the **thoracic and lumbar regions (T1 to L2)** of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones.
Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate. In most cases, the preganglionic nerve endings of the sympathetic nervous system are **highly branched**, enabling one preganglionic neuron to interact with many postganglionic neurons. **This arrangement enables this division to activate numerous effector organs at the same time.**
[Note: **The adrenal medulla**, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. The adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, secretes epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the blood].


SYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
EFFECTORS
PARASYMPATHETIC DIVISION
Brain, brain stem, and spinal cord
Lacrimal gland
Eye
Salivary glands
Trachea
Lungs
Heart
Liver
Text
Stomach
Pancreas
Intestines
Kidney
Bladder
Reproductive organs
Ganglia
Cranial
Cervical
Thoracic
Lumbar
Sacral
Sympathetic chain
Collateral ganglia
Sympathetic preganglionic fibers
Sympathetic postganglionic fibers
Parasympathetic preganglionic fibers
Parasympathetic postganglionic fibers

4. Parasympathetic neurons:

The parasympathetic preganglionic fibers **arise** from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs.

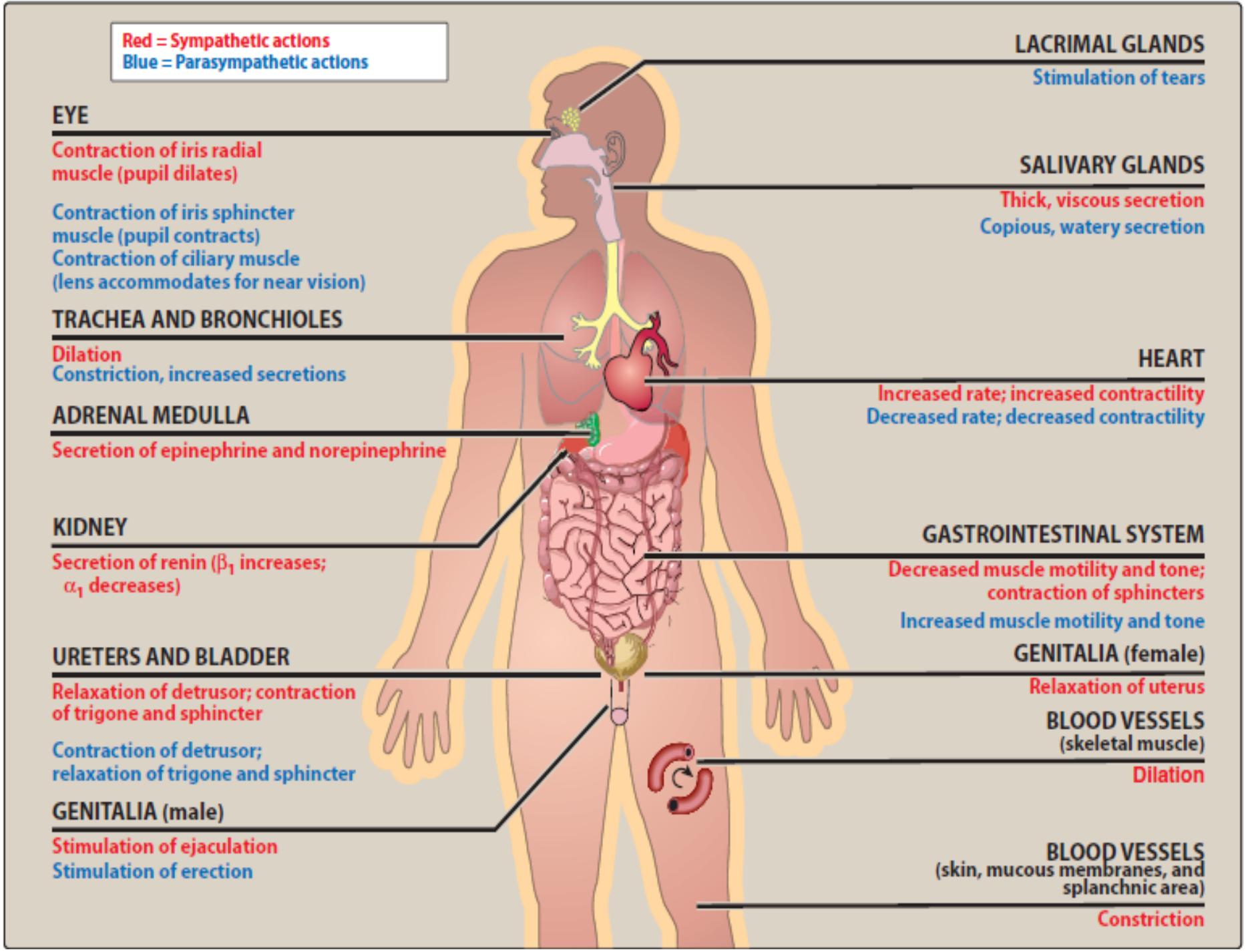
Thus, in contrast to the sympathetic system, the **preganglionic fibers are long**, and the **postganglionic ones are short**, with the ganglia close to or within the organ innervated. In most instances, there is a **one-to-one** connection between the preganglionic and postganglionic neurons, enabling **discrete response** of this system.

5. Enteric neurons:

The enteric nervous system is the **third division** of the ANS. It is a **collection** of nerve fibers that **innervate** the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the "**brain of the gut**."

This system functions **independently** of the CNS and **controls the motility, exocrine and endocrine secretions, and microcirculation of the GI tract**.

It is modulated by both the sympathetic and parasympathetic nervous systems.



Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise.

1. Effects of stimulation of the sympathetic division:

The **effect** of sympathetic output is to **increase** heart rate and blood pressure, to **mobilize** energy stores of the body, and to **increase** blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs.

Sympathetic stimulation results in **dilation** of the pupils and the bronchioles. It also **affects** GI motility and the function of the bladder and sexual organs.

2. Fight-or-flight response:

The changes experienced by the body during emergencies are referred to as the "**fight or flight**" response. These reactions are **triggered both** by direct sympathetic activation of the **effector organs** and by stimulation of the **adrenal medulla** to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors.

The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear. This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it is not essential for survival, it is nevertheless an important system that prepares the body to handle uncertain situations and unexpected stimuli.

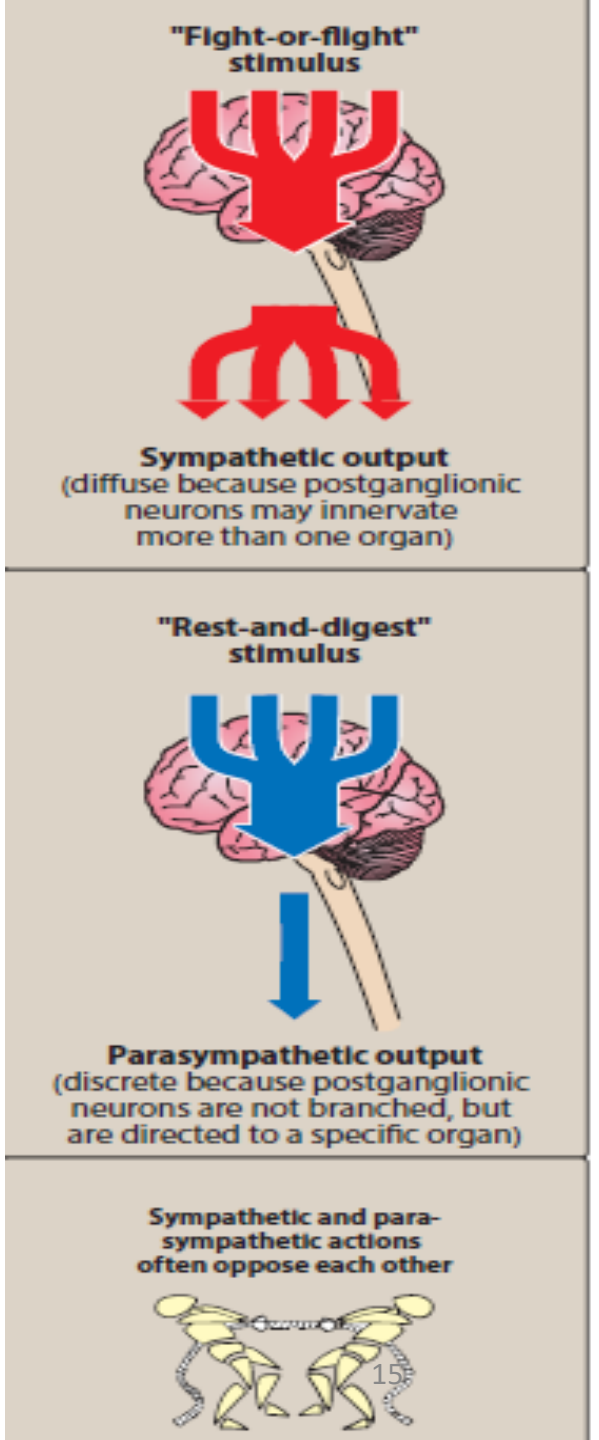
Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining **homeostasis** within the body. It is **required** for life, since it maintains essential bodily functions, **such as digestion and elimination of wastes.**

The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in "**rest-and-digest**" situations.

Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce **massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation.**

Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.



Role of the CNS in the control of autonomic functions

Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the current state of the body.
This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord.
These centers respond to the stimuli by sending out efferent reflex impulses via the ANS.

Innervation by the ANS

1. Dual innervation:

Most organs in the body are innervated by both divisions of the ANS. Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases the heart rate. Despite this dual innervation, one system usually predominates.
Sympathetic and parasympathetic actions are elicited by different stimuli. controlling the activity of a given organ.
For example, in the heart, the vagus nerve is the **predominant** factor for controlling rate. This type of antagonism is considered to be **dynamic and is fine-tuned continually to control homeostatic organ functions.**

2. Sympathetic innervation:

Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

Somatic nervous system

The efferent somatic nervous system **differs** from the ANS in that a **single myelinated** motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia.

Somatic nervous system is under **voluntary control**, whereas the **ANS is involuntary**.

Responses in the somatic division are generally **faster** than those in the ANS.

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division.

The sympathetic nervous system is **widely distributed**, innervating practically all effector systems in the body. By contrast, the distribution of the parasympathetic division is **more limited**.

The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization permits a diffuse discharge of the sympathetic nervous system. The parasympathetic division is more circumscribed, with mostly one-to-one interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells.

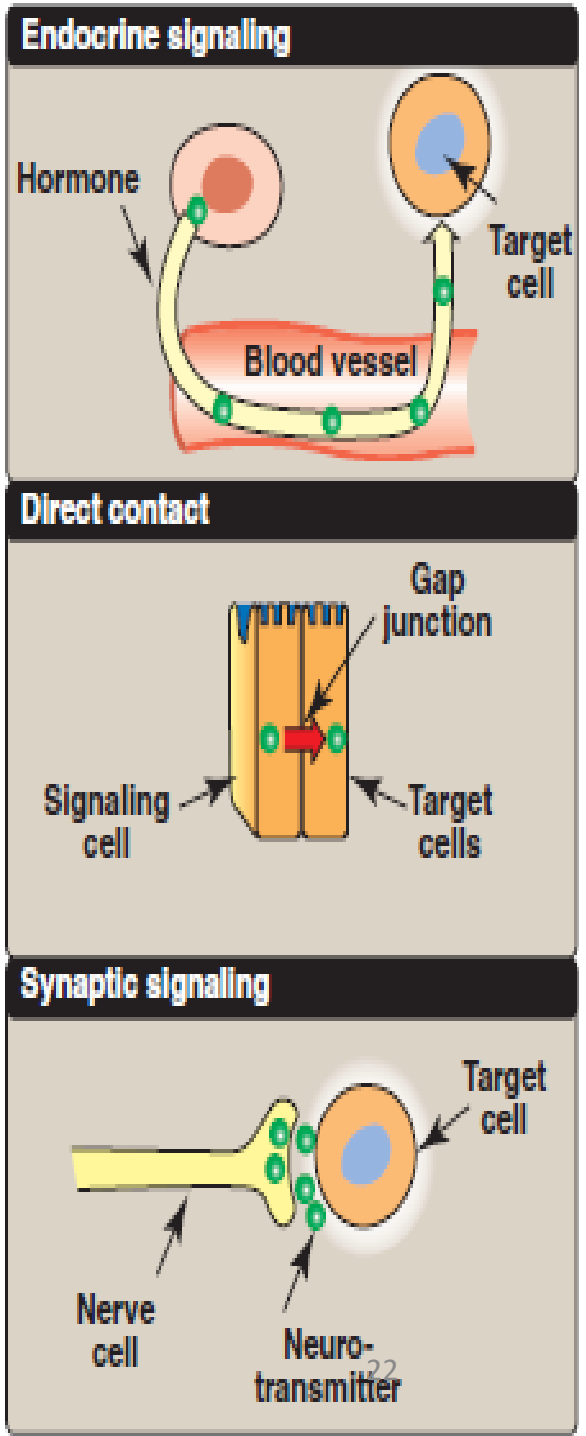
In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators.

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells.

B. Local mediators

Most cells in the body secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are **rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body.** Histamine and the prostaglandins are examples of local mediators.



C. Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals.
This release is triggered by the arrival of the **action potential** at the nerve ending, leading to **depolarization**.
An increase in **intracellular Ca2+** initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents.
The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

1. Membrane receptors:

All neurotransmitters, and most hormones and local mediators, are **too hydrophilic** to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs.

2. Types of neurotransmitters:

Although over 50 signal molecules in the nervous system have been identified, **norepinephrine** (and the closely related **epinephrine**), **acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid** are most commonly involved in the actions of therapeutically useful drugs.
Each of these chemical signals binds to a specific family of receptors.
Acetylcholine and norepinephrine are the primary chemical signals in the **ANS**, whereas a wide variety of neurotransmitters function in the CNS.

a. Acetylcholine:

The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released.

If transmission is mediated by **acetylcholine**, the neuron is termed **cholinergic**.

Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla.

Transmission from the autonomic **postganglionic** nerves to the effector organs in the **parasympathetic** system also involves the release of **acetylcholine**.

In the **somatic nervous system**, transmission at the **neuromuscular junction** (the junction of nerve fibers and voluntary muscles) is also **cholinergic**.

b. Norepinephrine and epinephrine:

When **norepinephrine and epinephrine** are the neurotransmitters, the fiber is termed **adrenergic**.

In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs.

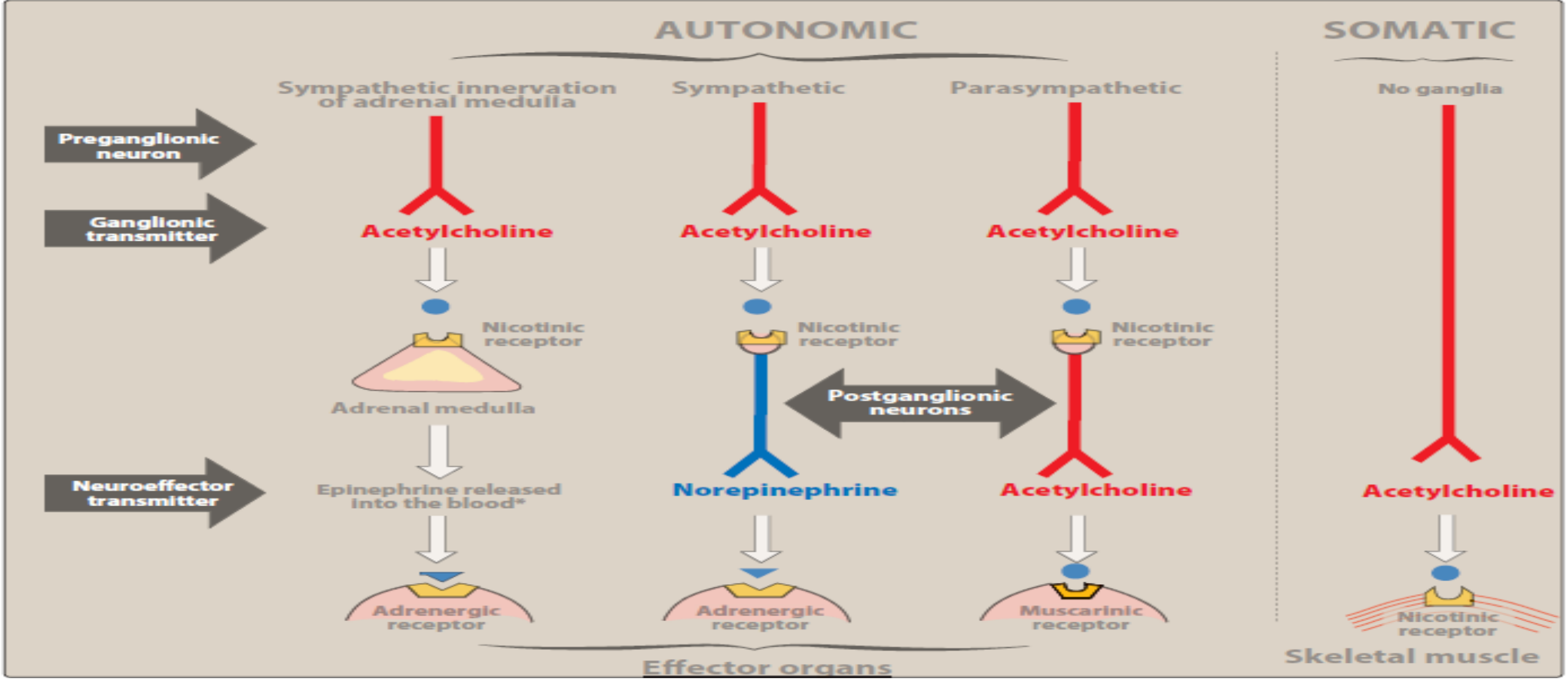


Figure 6: Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems. Cholinergic neurons are shown in red and adrenergic neurons in blue. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that, the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.]
*Epinephrine 80% and norepinephrine 20% released from adrenal medulla.

SIGNAL TRANSDUCTION IN THE EFFECTOR CELL

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the **phosphorylation of intracellular proteins or changes in the conductivity of ion channels.**
A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer.
Second messenger molecules produced in response to a neurotransmitter binding to a receptor translate the extracellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell.

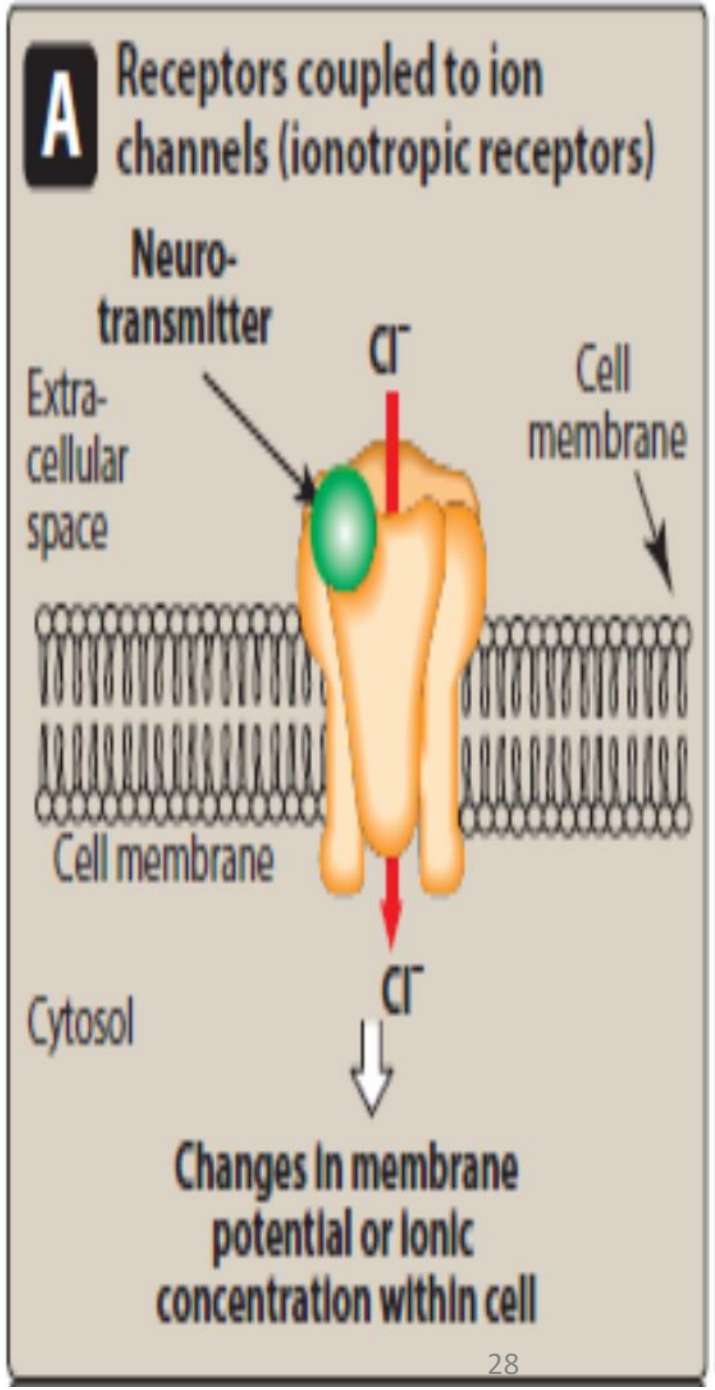
A. Membrane receptors affecting ion permeability (ionotropic receptors)

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules.

Some receptors, such as the **postsynaptic nicotinic receptors in the skeletal muscle cells**, are directly linked to membrane ion channels.

Therefore, **binding of the neurotransmitter occurs rapidly** (within fractions of a millisecond) and directly affects ion permeability.

These types of receptors are known as ionotropic receptors.



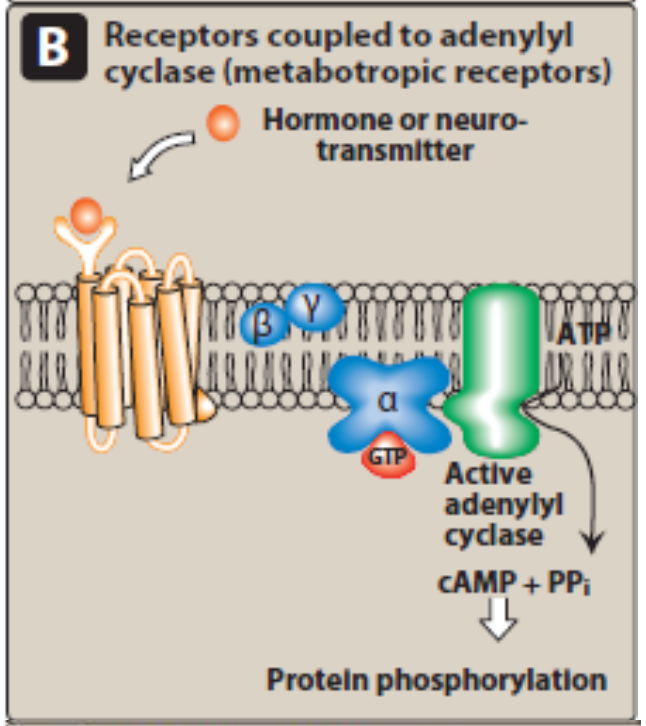
B. Membrane receptors coupled to second messengers (metabotropic receptors)

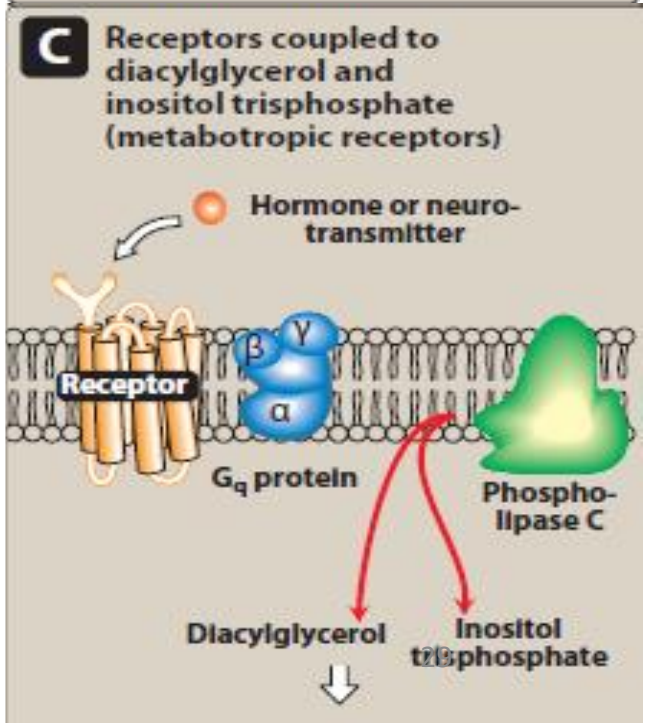
Many receptors are not directly coupled to ion channels. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result in a specific intracellular response.

Second messenger molecules, so **named** because they intervene **between the original message** (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translate neurotransmitter binding into a cellular response, usually through the intervention of a G protein.

The **two** most widely recognized second messengers are the **adenylyl cyclase system and the calcium/phosphatidylinositol system.**

The receptors coupled to the second messenger system are known as **metabotropic receptors**. **Muscarinic and adrenergic** receptors are examples of metabotropic receptors.





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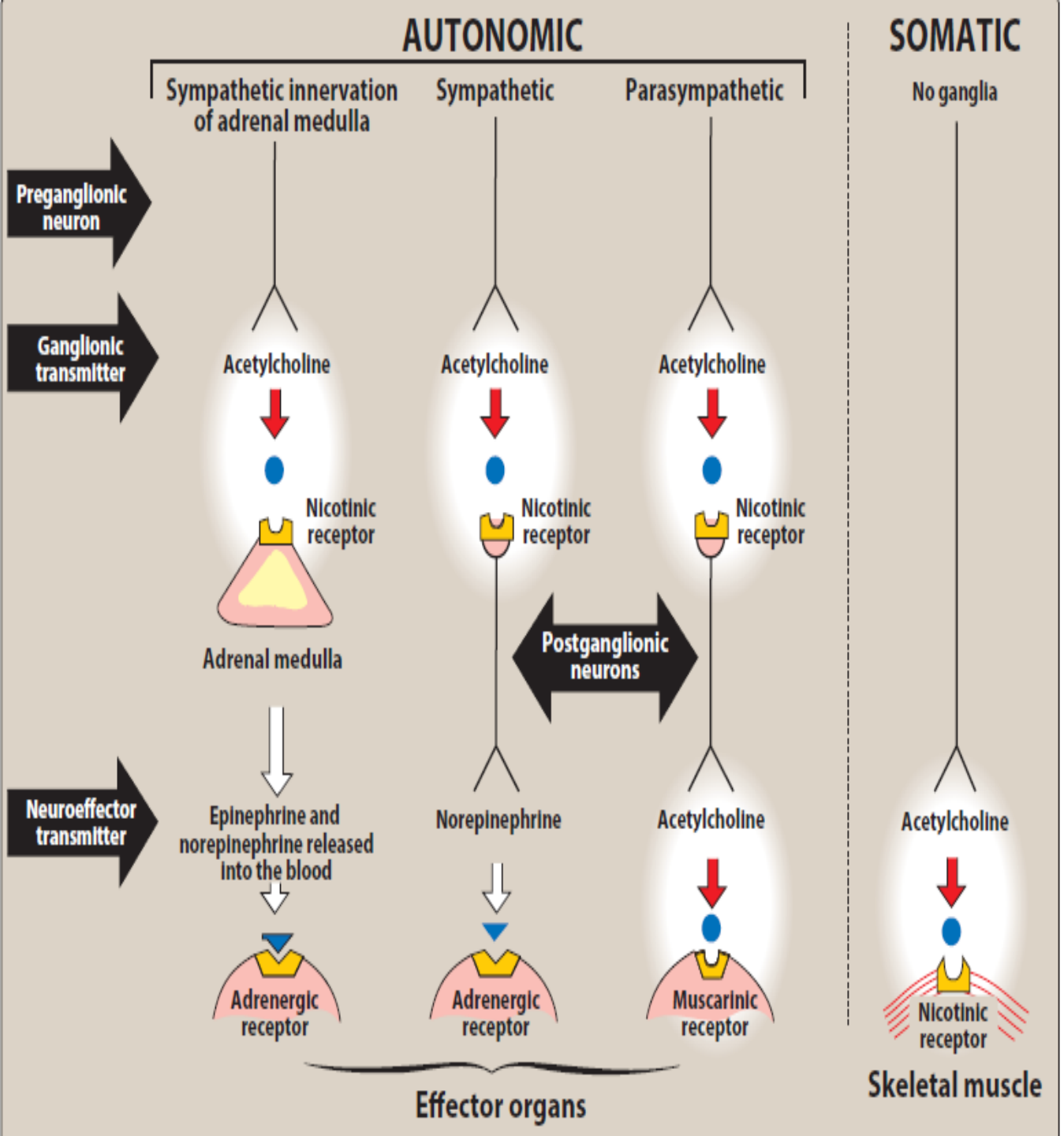


Cholinergic Agonists

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action.

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter.

The postganglionic sympathetic division of **sweat glands** also uses acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in the central nervous system (CNS).

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps:

1) synthesis,

2) storage,

3) release,

4) binding of ACh to a receptor,

5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and

6) recycling of choline and acetate.

1. Synthesis of acetylcholine:

Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an **energy-dependent carrier system** that cotransports **sodium** and can be **inhibited** by the drug **hemicholinium.**
[Note: Choline has a **quaternary nitrogen** and carries a permanent **positive** charge and, thus, **cannot** diffuse through the membrane.]
The **uptake** of choline is the **rate limiting step** in ACh synthesis.
Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2. Storage of acetylcholine in vesicles:

ACh is packaged and stored into **presynaptic vesicles** by an active transport process. The mature vesicle contains not only ACh but also **adenosine triphosphate (ATP) and proteoglycan**.
Co- transmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles contain the **primary** neurotransmitter (here, **ACh**) as well as a **co-transmitter** (here, **ATP**) that increases or decreases the effect of the primary neurotransmitter.

3. Release of acetylcholine:

When an action potential propagated by **voltage-sensitive sodium channels** arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium.
Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space. **This release can be blocked by botulinum toxin.** In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

4. Binding to the receptor:

ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors.
The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: **muscarinic and nicotinic.**
Binding to a receptor leads to a biologic response within the cell, such as the **initiation** of a nerve impulse in a postganglionic fiber or **activation** of specific enzymes in effector cells, as mediated by second messenger molecules.

5. Degradation of acetylcholine:

The signal at the postjunctional effector site is rapidly terminated because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft.

6. Recycling of choline:

Choline may be recaptured by a **sodium-coupled,** high-affinity uptake system that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

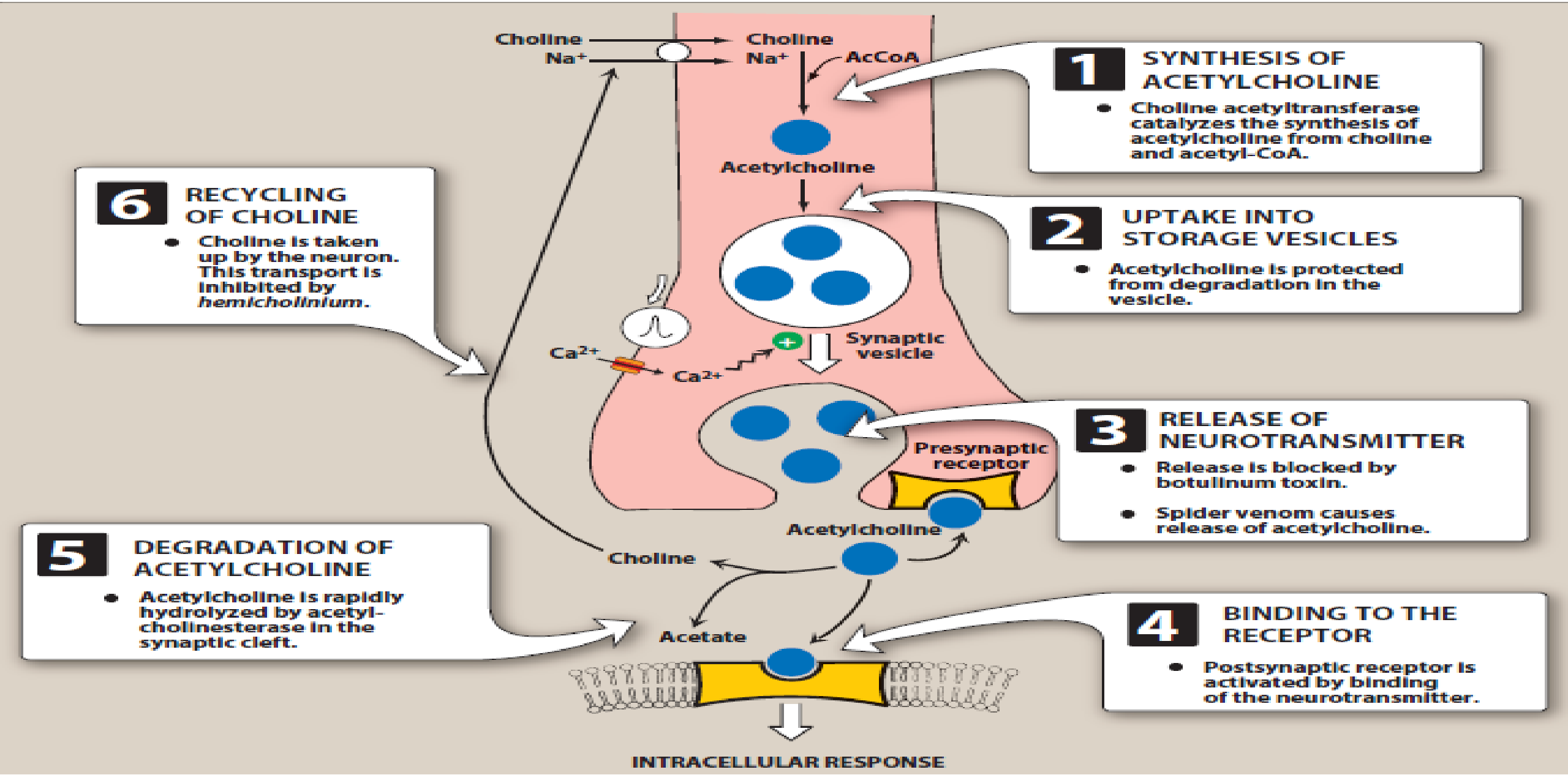
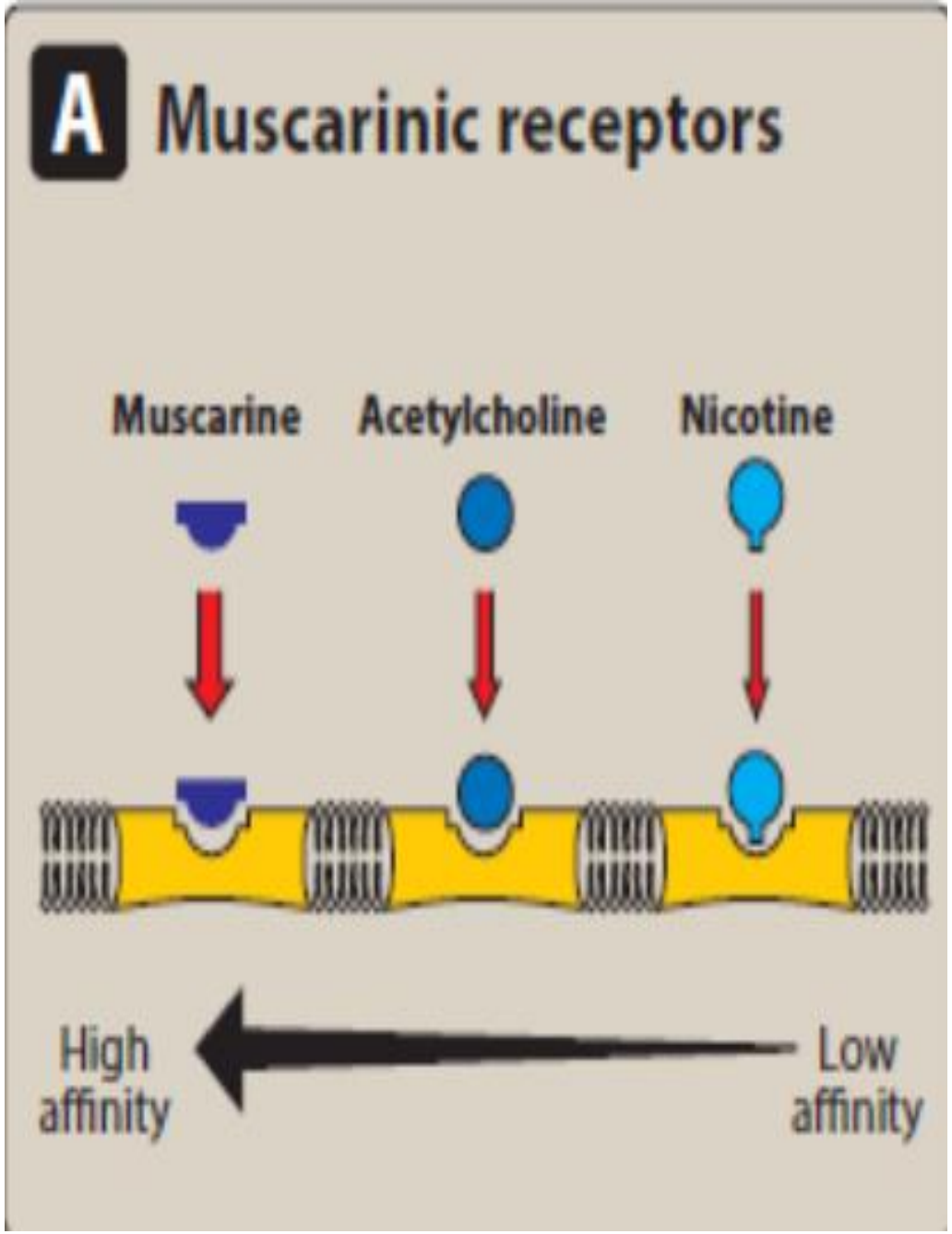


Figure 2: Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (**cholinomimetic agents**).



A. Muscarinic receptors

Muscarinic receptors belong to the class of **G protein**–coupled receptors (**metabotropic receptors**).

These receptors, in addition to binding ACh, also recognize **muscarine**, an alkaloid that is present in **certain poisonous mushrooms**. In contrast, the muscarinic receptors show only a **weak affinity** for nicotine. There are **five** subclasses of muscarinic receptors. However, only M1, M2, and M3 receptors have been functionally characterized.

1.Locations of muscarinic receptors:

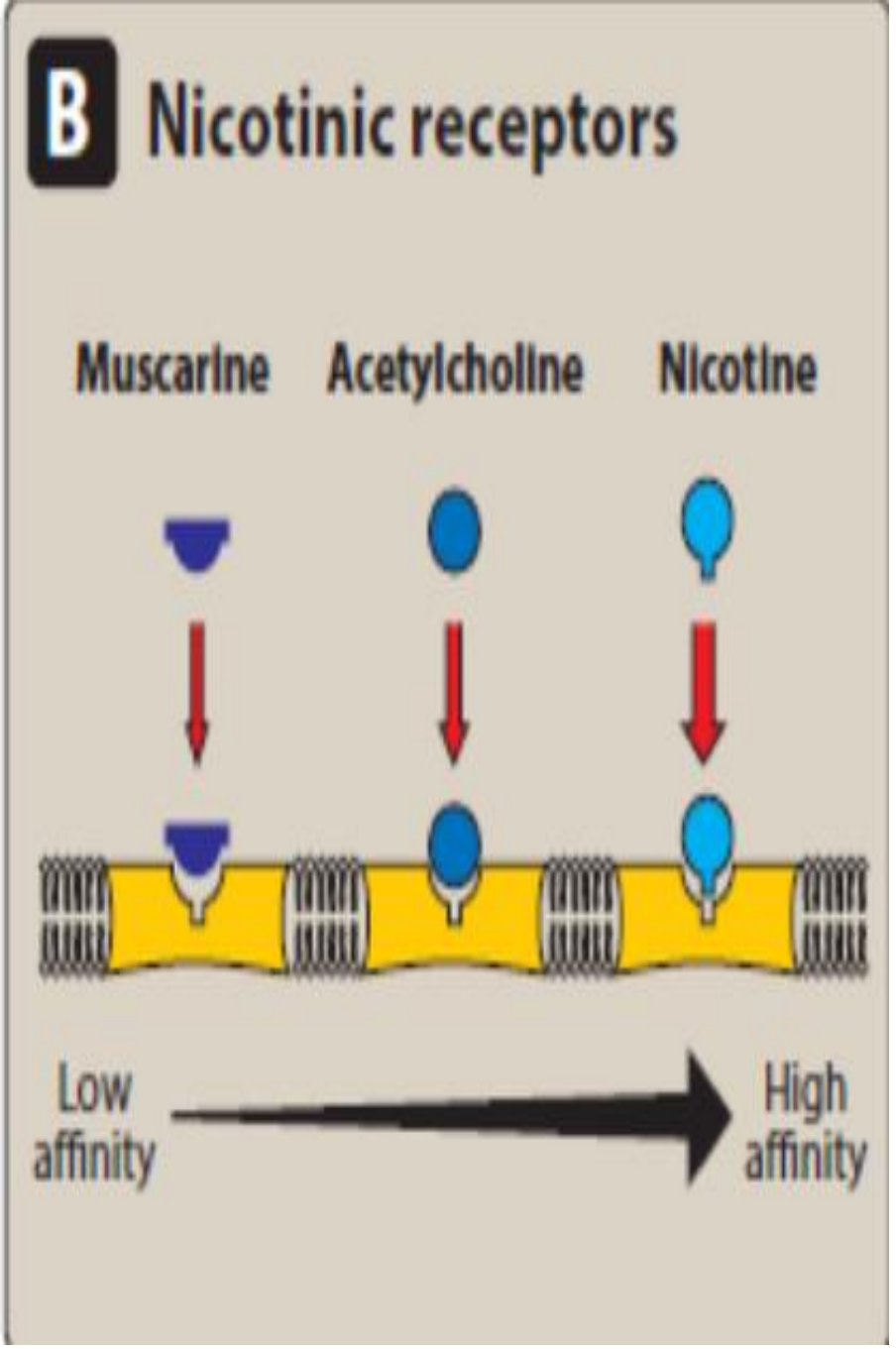
These receptors are found on the autonomic effector organs, such as the **heart, smooth muscle, brain, and exocrine glands**. Although all five subtypes are found on neurons, M1 receptors are also found on **gastric parietal cells**, M2 receptors on **cardiac** cells and **smooth** muscle, and M3 receptors on the **bladder, exocrine glands, and smooth muscle.**

2. Mechanisms of acetylcholine signal transduction:

A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when M1 or M3 receptors are **activated**, the receptor undergoes a conformational change and interacts with a G protein, designated **Gq**, that in turn **activates** phospholipase C. This ultimately leads to the **production** of the second messenger inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 causes an **increase** in intracellular **Ca2+.** Calcium can then interact to stimulate or inhibit enzymes or to cause **hyperpolarization, secretion, or contraction**. Diacylglycerol activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell. In contrast, **activation of the M2** subtype on the cardiac muscle stimulates a G protein, designated Gi, that inhibits adenylyl cyclase and increases K+ conductance. The heart responds with a **decrease in rate and force of contraction.**

3. Muscarinic agonists:

Pilocarpine is an example of a **nonselective** muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer's disease and M3 receptor antagonists for the treatment of chronic obstructive pulmonary disease.



B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine. The nicotinic receptor is composed of **five subunits**, and it functions as a **ligand-gated ion channel**. Binding of two ACh molecules elicits a conformational change that allows the entry of **sodium ions**, resulting in the **depolarization** of the effector cell. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, the **adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles**. Those at the NMJ are sometimes designated NM, and the others, NN. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, **ganglionic receptors are selectively blocked by mecamylamine, whereas NMJ receptors are specifically blocked by atracurium.**

DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic). These agents may be broadly classified into two groups:

1) endogenous choline esters, which include **Ach and synthetic esters of choline, such as carbachol and bethanechol**, and

2) naturally occurring alkaloids, such as **nicotine and pilocarpine**.

All of the direct-acting cholinergic drugs have a **longer duration** of action than ACh.

The more therapeutically useful drugs (**pilocarpine & bethanechol**) preferentially bind to muscarinic receptors and are sometimes referred to as **muscarinic agents**. However, as a group, the direct-acting agonists show **little specificity** in their actions, which **limits** their clinical usefulness.

A. Acetylcholine

Acetylcholine is a **quaternary ammonium** compound that **cannot** penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (**leading to diffuse effects**) and its **rapid inactivation by the cholinesterases**. ACh has both muscarinic and nicotinic activity. Its actions include the following:

1. Decrease in heart rate and cardiac output:

The actions of Ach on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in **cardiac rate (negative chronotropy**) and stroke volume as a result of a **reduction** in the rate of firing at the sinoatrial (SA) node. **[Note: Normal vagal activity regulates the heart by the release of ACh at the SA node.]**

2. Decrease in blood pressure:

Injection of ACh causes vasodilation and lowering of blood pressure by an **indirect** mechanism of action. ACh activates **M3** receptors found on **endothelial cells** lining the smooth muscles of blood vessels. This results in the production of **nitric oxide from arginine**. Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase-3 inhibition. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. **Atropine blocks these muscarinic receptors and prevents ACh from producing vasodilation.**

3. Other actions:

In the gastrointestinal {GI) tract, acetylcholine **increases** salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions and causes **bronchoconstriction**. [Note: **Methacholine**, a direct-acting cholinergic agonist, is used to assist in the **diagnosis** of asthma due to its bronchoconstricting properties.] In the genitourinary tract, Ach **increases** the tone of the detrusor muscle, causing **urination**. In the eye, ACh is involved in stimulation of ciliary muscle contraction for **near vision** and in the constriction of the pupillae sphincter muscle, causing **miosis** (marked constriction of the pupil). ACh {1% solution) is instilled into the anterior chamber of the eye to **produce miosis during ophthalmic surgery**.

B. Bethanechol

Bethanechol is an unsubstituted **carbamoyl ester**, structurally related to ACh.
It **is not hydrolyzed** by AChE due to the **esterification of carbamic acid**, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to the addition of the methyl group) but does have strong **muscarinic activity**. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action.

1. Actions:

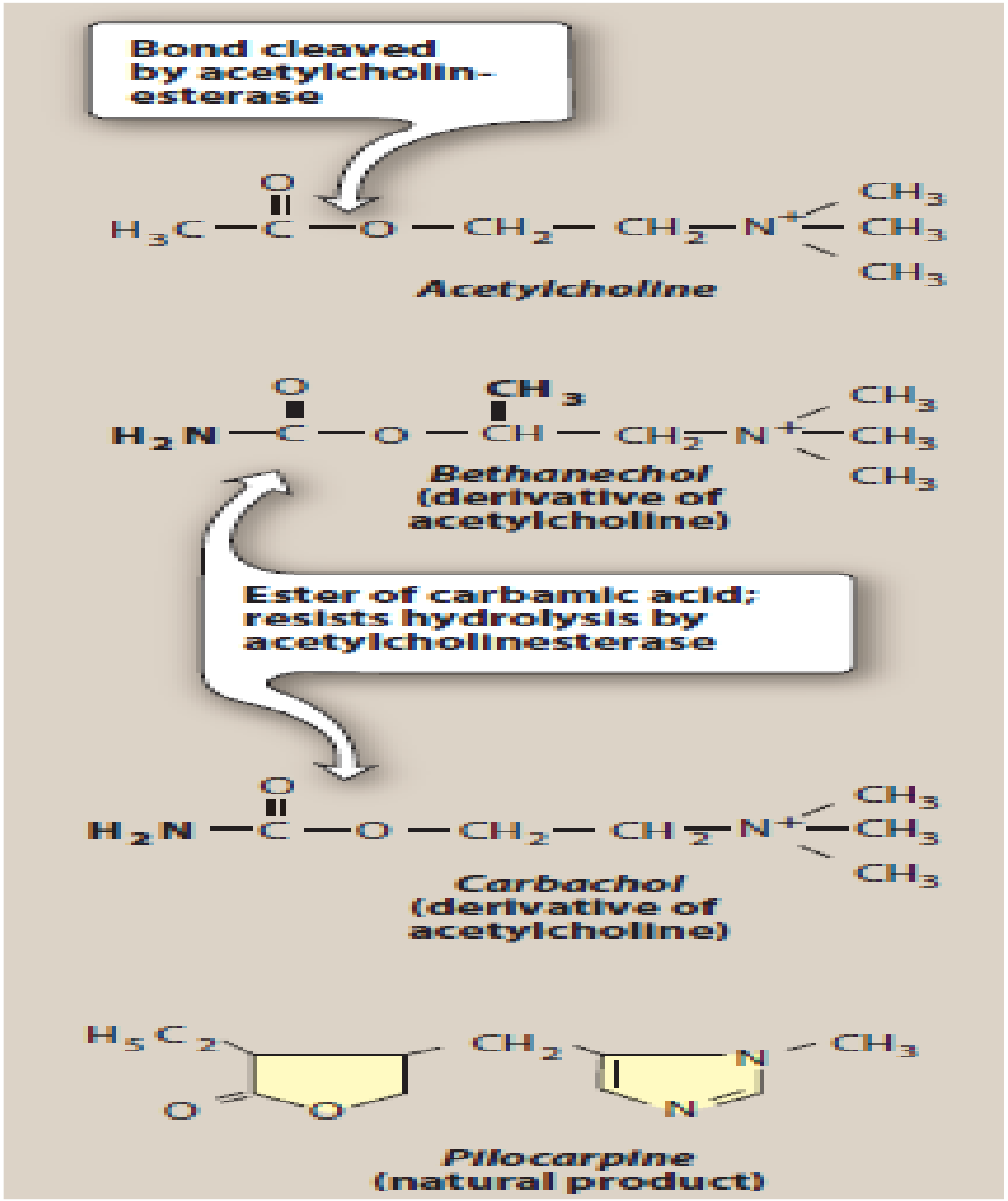
Bethanechol directly stimulates muscarinic receptors, causing **increased intestinal motility and tone.** It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects **produce urination**.

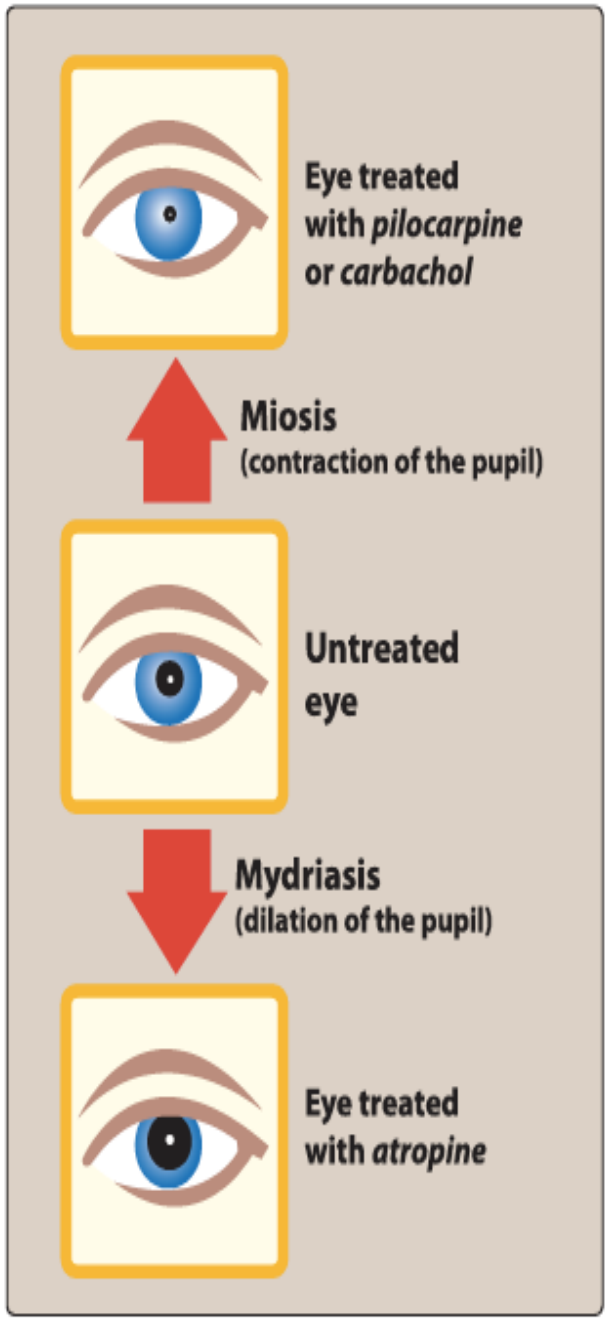
2. Therapeutic applications:

In urologic treatment, bethanechol is used to stimulate the **atonic bladder**, particularly in **postpartum or postoperative, nonobstructive urinary retention**.

3. Adverse effects:

Bethanechol causes the effects of generalized cholinergic stimulation.
These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. **Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.**


Bond cleaved by acetylcholin-esterase
Acetylcholine
Bethanechol (derivative of acetylcholine)
Ester of carbamic acid; resists hydrolysis by acetylcholinesterase
Carbachol (derivative of acetylcholine)
Pilocarpine (natural product)



C. Carbachol (carbamylcholine)

Carbachol has both **muscarinic and nicotinic actions**. Like bethanechol, carbachol is an ester of carbamic acid and a poor substrate for AChE. It is biotransformed by other esterases, but at a much slower rate.

1. Actions:

Carbachol has profound effects on both the cardiovascular and GI systems because of its **ganglion-stimulating activity**, and it may **first stimulate and then depress** these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing **miosis and a spasm of accommodation** in which the ciliary muscle of the eye remains in a constant state of contraction. The vision becomes fixed at some particular distance, making it impossible to focus.

2. Therapeutic uses:

Because of its **high potency, receptor nonselectivity, and relatively long duration of action,** carbachol is rarely used therapeutically **except** in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.

3. Adverse effects:

At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).

D. Pilocarpine

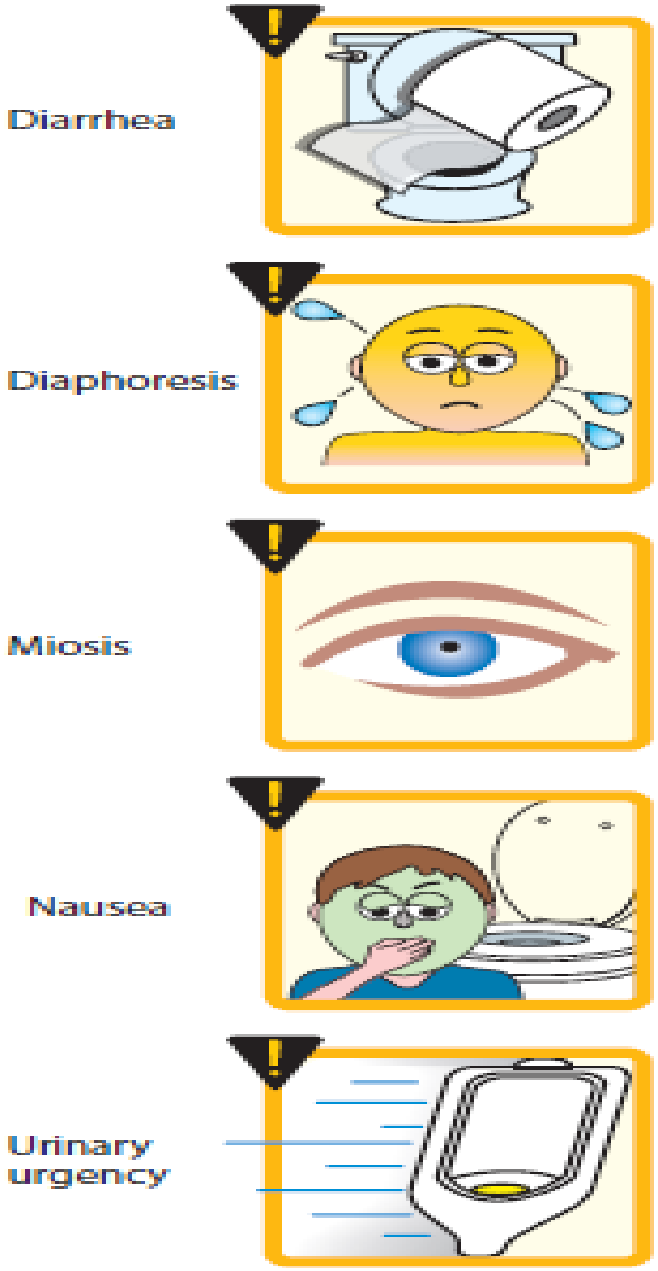
The alkaloid pilocarpine is a **tertiary amine** and is stable to hydrolysis by AChE. Compared with ACh and its derivatives, it is far less potent but is **uncharged and can penetrate the CNS at therapeutic doses**. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

1. Actions:

Applied topically to the eye, pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. **Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.**

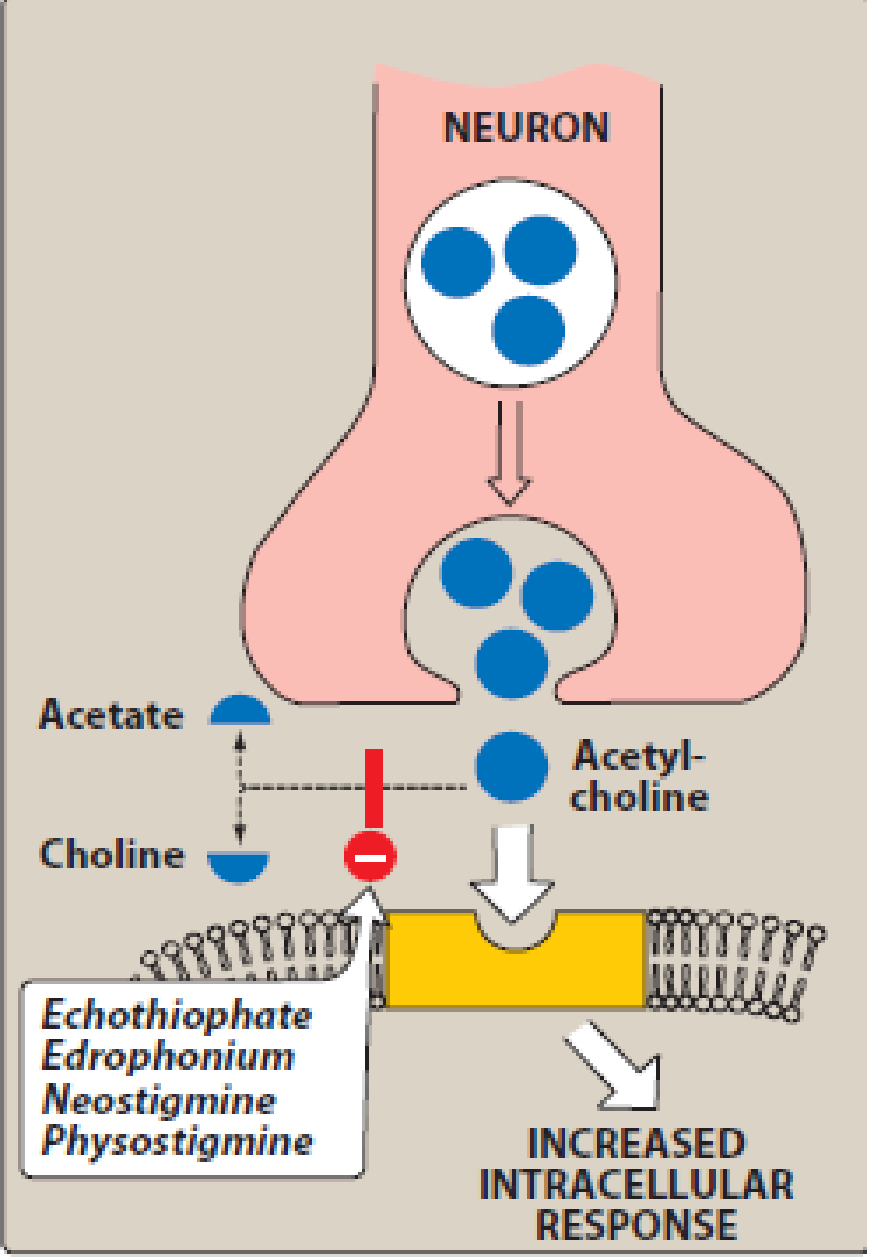
2. Therapeutic use in glaucoma:

Pilocarpine is used to treat glaucoma and is the drug of choice for **emergency lowering of intraocular pressure of both open-angle and angle-closure glaucoma.** Pilocarpine is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts **4 to 8 hours**, and can be repeated. [Note: Topical carbonic anhydrase inhibitors, such as dorzolamide and B-adrenergic blockers such as timolol, are **effective** in treating glaucoma but are **not used** for emergency lowering of intraocular pressure.] The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine. The drug is beneficial in promoting salivation in patients with **xerostomia** resulting from irradiation of the head and neck. Sjogren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and **cevimeline**, a cholinergic drug that also has the drawback of being nonspecific.



3. Adverse effects:

Pilocarpine can cause blurred vision, night blindness, and brow ache. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. The effects are similar to those produced by consumption of mushrooms of the genus Inocybe, which contain muscarine. **Parenteral atropine, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of pilocarpine.**



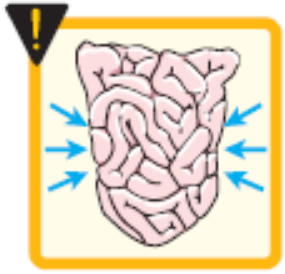
Mechanisms of action of indirect cholinergic agonists

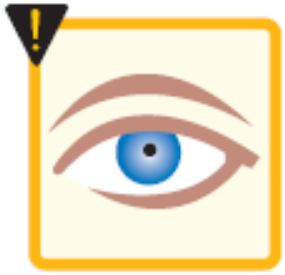
ANTICHOLINESTERASE AGENTS (REVERSIBLE)

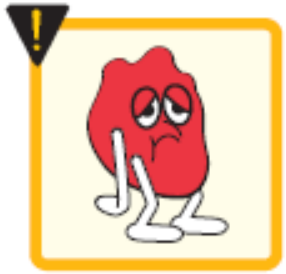
AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. Therefore, these drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain. The reversible AChE inhibitors can be broadly **classified as short acting or intermediate-acting agents**.

A. Edrophonium

Edrophonium is the prototype short-acting AChE inhibitor. Edrophonium binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It is rapidly absorbed and has a short duration of action of 10 to 20 minutes due to rapid renal elimination. Edrophonium is a quaternary amine, and its actions are limited to the periphery. It is used in the **diagnosis of myasthenia gravis,** an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes their degradation, making fewer receptors available for interaction with Ach. Intravenous injection of edrophonium leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote). Edrophonium may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers (NMBs) after surgery. Due to the availability of other agents, edrophonium use has become limited.







Some actions of physostigmine.

B. Physostigmine

Physostigmine is a **nitrogenous carbamic acid ester** found naturally in plants and is a **tertiary amine**. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. Actions:

Physostigmine has a wide range of effects and stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of Gl smooth muscles, miosis, bradycardia, and hypotension. **Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses).** Its duration of action is about 30 minutes to 2 hours, and it is considered an intermediate-acting agent. Physostigmine can enter and stimulate the cholinergic sites in the CNS.

2. Therapeutic uses:

Physostigmine is used in the treatment of **overdoses of drugs with anticholinergic actions, such as atropine, and to reverse the effects of NMBs**.

3. Adverse effects:

High doses of physostigmine may lead to convulsions. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the NMJ causes the accumulation of Ach and, ultimately through continuous depolarization, results in paralysis of skeletal muscle. However, **these effects are rarely seen with therapeutic doses.**

C. Neostigmine

Neostigmine is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to that of physostigmine.

1. Actions:

Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. **Its effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes.** Neostigmine has an intermediate duration of action, usually 30 minutes to 2 hours.

2. Therapeutic uses:

It is used to **stimulate the bladder and GI tract** and also as an **antidote** for competitive neuromuscular-blocking agents. Neostigmine is also used to manage symptoms of **myasthenia gravis**.

3. Adverse effects:

Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

D. Pyridostigmine

Pyridostigmine is another cholinesterase inhibitor used in the **chronic management of myasthenia gravis**. Its duration of action is intermediate (3 to 6 hours) but **longer** than that of neostigmine. Adverse effects are similar to those of neostigmine.

E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. Tacrine, the first agent in this category, has been replaced by others because of its hepatotoxicity. Despite the ability of donepezil, rivastigmine, and galantamine to delay the progression of Alzheimer disease, none can stop its progression. **GI distress** is their primary adverse effect.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the capacity to bind **covalently** to AChE. The result is a long-lasting increase in Ach at all sites where it is released. Many of these drugs are extremely toxic and were **developed by the military as nerve agents**. Related compounds, such as parathion and malathion, are used as insecticides.

A. Echothiophate

1. Mechanism of action:

Echothiophate is an organophosphate that covalently binds via its phosphate group at the active site of AChE. Once this occurs, the enzyme is permanently inactivated, and **restoration of AChE activity requires the synthesis of new enzyme molecules**. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called **aging**, makes it impossible for **chemical reactivators, such as pralidoxime**, to break the bond between the remaining drug and the enzyme.

2. Actions:

Actions include generalized cholinergic stimulation, paralysis of motor function **(causing breathing difficulties),** and **convulsions**. Echothiophate produces intense miosis and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of outflow of aqueous humor. **Atropine** in high dosages can reverse many of the peripheral and some of the central muscarinic effects of echothiophate.

3. Therapeutic uses:

A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. However, echothiophate is rarely used due to its side effect profile, which includes the risk of **cataracts**.

TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides, which has led to numerous cases of accidental poisoning with these agents.
In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as **sarin** are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (**cholinergic crisis**). Depending on the agent, the effects can be peripheral or can affect the whole body.

Reactivation of acetylcholinesterase

Pralidoxime (2-PAM) can reactivate inhibited AChE. However, it is **unable to penetrate into the CNS** and therefore is not useful in treating the CNS effects of organophosphates.
The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme.
If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects. With the newer nerve agents that produce **aging** of the enzyme complex within seconds, **pralidoxime is less effective.** Pralidoxime is a weak AChE inhibitor and, at higher doses, may cause side effects similar to other AChE inhibitors. In addition, it **cannot overcome toxicity** of reversible AChE inhibitors (for example, physostigmine).

Other treatments:

Atropine is administered to prevent muscarinic side effects of these agents. Such effects include **increased bronchial and salivary secretion, bronchoconstriction, and bradycardia**.
Diazepam is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

Autonomic Nervous System
Cholinergic Antagonists

Tikrit University

College of Pharmacy

Department of Pharmacology and Toxicology

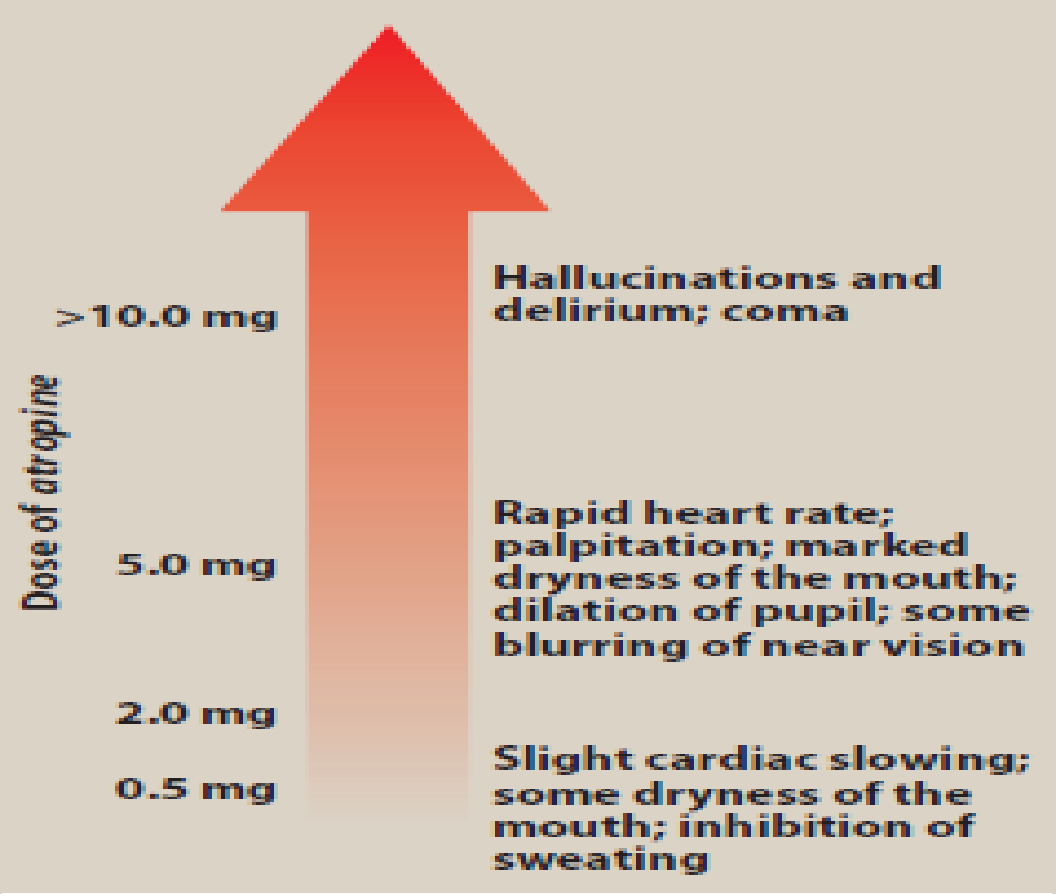
Ass. Lec. Rabei Abdullah Salih

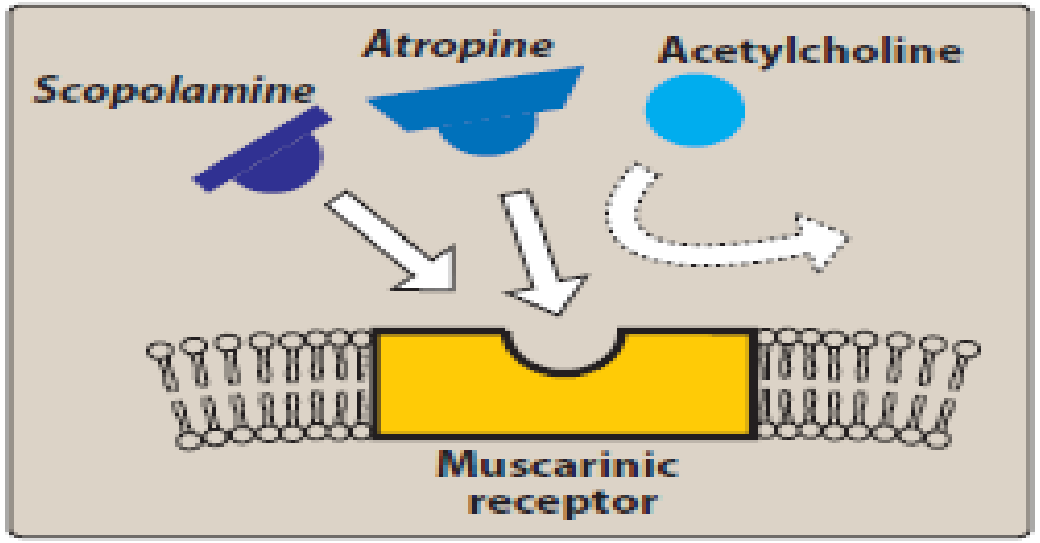
Cholinergic antagonist

Cholinergic antagonist is a general term for agents that **bind** to cholinoceptors (muscarinic or nicotinic) and **prevent the effects of acetylcholine (ACh) and other cholinergic agonists.**
The most clinically useful of these agents are selective blockers of muscarinic receptors.
They are commonly **known** as **anticholinergic agents** (a misnomer, as they antagonize only muscarinic receptors), **antimuscarinic agents** (more accurate terminology), or **parasympatholytics**.
A **second group** of drugs, the **ganglionic blockers**, shows a preference for the nicotinic receptors of the **sympathetic and parasympathetic ganglia**.
Clinically, they are the **least** important of the cholinergic antagonists.
A **third family** of compounds, the **neuromuscular blocking agents** (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles.
These drugs are used as **skeletal muscle relaxants** in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients.

ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, **atropine and scopolamine**) **block muscarinic receptors, causing inhibition of muscarinic functions.** In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they don't block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have **little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia**. The anticholinergic drugs are beneficial in a variety of clinical situations.





A. Atropine:

Atropine is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors.

It binds **competitively** and prevents ACh from binding to those sites.

Atropine acts both centrally and peripherally.

Its general actions last about 4 hours, except when placed **topically in the eye**, where the action may last for days.

Neuroeffector organs have varying sensitivity to atropine. **The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva and the heart**.

1. Actions:

a. Eye:

Atropine blocks muscarinic activity in the eye, resulting in **mydriasis** (dilation of the pupil), unresponsiveness to light, and **cycloplegia** (inability to focus for near vision).

In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

b. Gastrointestinal (GI):

Atropine can be used as an **antispasmodic** to reduce activity of the GI tract. Atropine and scopolamine are probably **the most potent antispasmodic drugs available**.

Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, atropine is not effective for the treatment of peptic ulcer.

Doses of atropine that **reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with atropine.**

c. Cardiovascular:

Atropine produces divergent effects on the cardiovascular system, depending on the dose.

At low doses, the predominant effect is a **slight decrease in heart rate.** This effect results from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased Ach release.

Higher doses of atropine cause a **progressive increase in heart rate** by blocking the M2 receptors on the sinoatrial node.

d. Secretions:

Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to atropine. **Sweat and lacrimal glands are similarly affected.**

2- Therapeutic uses:

a. Ophthalmic:

Topical atropine exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors **without** interference by the accommodative capacity of the eye. **Shorter-acting antimuscarinics** (cyclopentolate and tropicamide) have largely **replaced** atropine due to prolonged mydriasis observed with atropine (**7 to 14 days vs. 6 to 24 hours with other agents**).

b. Antispasmodic:

Atropine is used as an antispasmodic agent to relax the GI tract.

c. Cardiovascular:

The drug is used to treat bradycardia of varying etiologies.

d. Antisecretory:

Atropine is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

e. Antidote for cholinergic agonists:

Atropine is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as **physostigmine**, and in some types of **mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases).**

Massive doses of atropine may be required over a long period of time to counteract the poisons. The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating **central toxic effects of anticholinesterases.**

3. Pharmacokinetics:

Atropine is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4. Adverse effects:

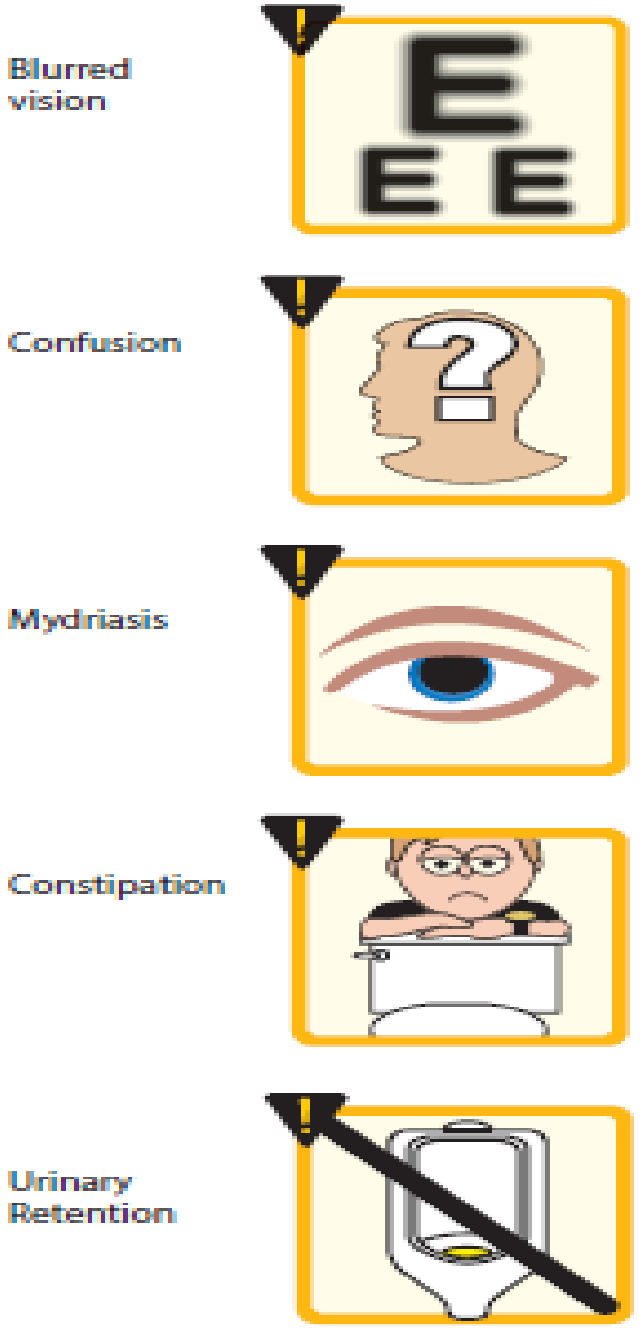
Depending on the dose, atropine may cause **dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation**.

Effects on the **CNS** include **restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death.**

Low doses of cholinesterase inhibitors, such as physostigmine, may be used to overcome atropine toxicity.

Atropine may also induce troublesome urinary retention. The drug may be **dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature**.

Figure 2: Adverse effects commonly observed with muscarinic antagonists



B. Scopolamine

Scopolamine, another tertiary amine plant alkaloid, produces peripheral effects similar to those of atropine. However, **scopolamine has greater action on the CNS** (unlike atropine, CNS effects are observed at therapeutic doses) and a **longer duration of action as compared to atropine.**

1. Actions:

Scopolamine is one of the **most effective anti–motion sickness** drugs available. It also has the **unusual effect of blocking short-term memory**.
In contrast to atropine, scopolamine produces sedation, but at higher doses, it can produce excitement. Scopolamine may produce euphoria and is susceptible to abuse.

2. Therapeutic uses:

The therapeutic use of scopolamine is **limited** to prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days.

3. Pharmacokinetics and adverse effects:

These aspects are similar to those of atropine, with the exception of longer half-life.

C. Aclidinium, glycopyrrolate, Ipratropium and tiotropium

Ipratropium and tiotropium are quaternary derivatives of atropine, and glycopyrrolate and aclidinium are **synthetic quaternary** compounds. Ipratropium is classified as a short-acting muscarinic antagonist (**SAMA**), while glycopyrrolate, tiotropium, and aclidinium are classified as long-acting muscarinic antagonists (**LAMAs**) **based on the duration of action.**

These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Ipratropium and tiotropium are **also used** in the **acute management of bronchospasm in asthma and chronic management of asthma, respectively.**

All of these agents are delivered via inhalation. **Because of the positive charge, these drugs don't enter the systemic circulation or the CNS, restricting effects to the pulmonary system.**

D. Tropicamide and cyclopentolate

These agents are used as **ophthalmic solutions for mydriasis and cycloplegia**. Their duration of action is **shorter than that of atropine**.
Tropicamide produces mydriasis for 6 hours and cyclopentolate for 24 hours.

E. Benztropine and trihexyphenidyl

Benztropine and trihexyphenidyl are useful as adjuncts with other antiparkinsonian agents to treat Parkinson's disease and other types of parkinsonian syndromes, including **antipsychotic-induced extrapyramidal** symptoms.

F. Oxybutynin and other antimuscarinic agents for overactive bladder:

Oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, and trospium are synthetic atropine-like drugs with antimuscarinic actions.

1. Actions

By **competitively** blocking muscarinic (M3) receptors in the bladder, **intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced**.
Antimuscarinic actions at M3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. Darifenacin and solifenacin are relatively **more selective M3** muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.

2. Therapeutic uses

These agents are used for management of overactive bladder and urinary incontinence. **Oxybutynin** is also used in patients with **neurogenic bladder**.

3. Pharmacokinetics

All of the agents are available in oral dosage forms. Most agents have a long half-life, which allows once-daily administration.
[Note: Immediate-release oxybutynin and tolterodine must be dosed two or more times daily; however, extended-release formulations of these agents allow for once-daily dosing.]
Oxybutynin is also available in a transdermal patch and topical gel formulation. These drugs are hepatically metabolized by the cytochrome P450 system (primarily CYP 3A4 and 2D6), with the **exception** of trospium, which is thought to undergo ester hydrolysis.

4. Adverse effects

Side effects include **dry mouth, constipation, and blurred vision**, which limit tolerability of these agents.
Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated.
Trospium is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia

Autonomic Nervous System
Ganglionic Blockers

Tikrit University

College of Pharmacy

Department of Pharmacology and Toxicology

Ass. Lec. Rabei Abdullah Salih

GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show **no selectivity** toward the parasympathetic or sympathetic ganglia and are **not effective** as neuromuscular antagonists.

Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor.

The responses of the nondepolarizing blockers are **complex and mostly unpredictable.** Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

Nicotine

A component of cigarette smoke, nicotine, is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health.

Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in **stimulation and then in paralysis of all ganglia**.

The stimulatory effects are complex and result from increased release of neurotransmitters, due to effects on both sympathetic and parasympathetic ganglia.

The overall response of a physiologic system is a **summation** of the stimulatory and inhibitory effects of nicotine.

These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and **increased peristalsis and secretions**.

At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.

NEUROMUSCULAR-BLOCKING AGENTS

These drugs block cholinergic transmission **between motor nerve endings and the nicotinic receptors on skeletal muscle.**

They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ.

Neuromuscular blockers (NMBs) are clinically **useful to facilitate rapid intubation when needed due to respiratory failure (rapid sequence intubation).**

During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses.

This increases the safety of anesthesia by allowing patients to **recover quickly and completely.** NMBs should not substitute for inadequate anesthesia.

NMBs are also used in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.

A. Nondepolarizing (competitive) blockers

The first known NMB was curare, which Amazon hunters used to paralyze prey. The development of tubocurarine followed, but it has been replaced by agents with fewer adverse effects, such as **cisatracurium, mivacurium, pancuronium, rocuronium, and vecuronium**

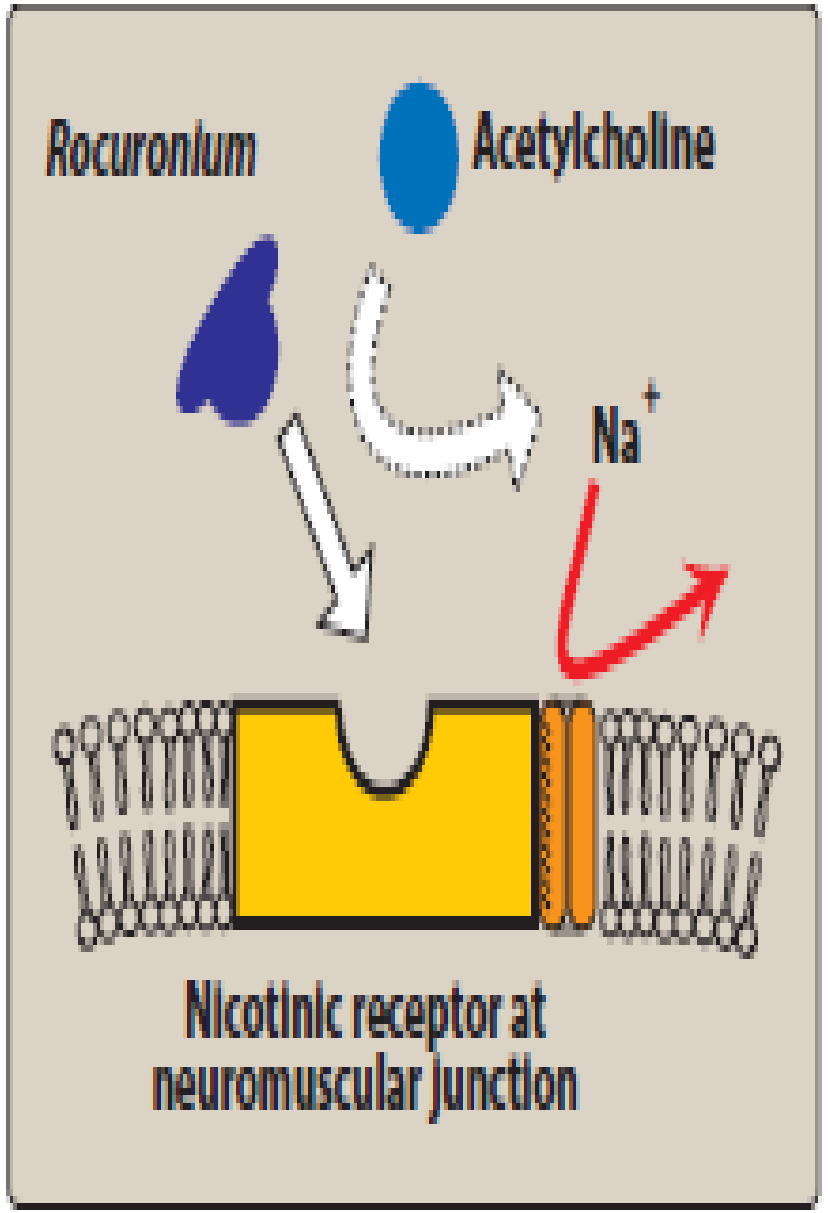


Figure 3: Mechanism of action of competitive neuromuscular-blocking drugs.

1. Mechanism of action:

a. At low doses:

Nondepolarizing agents competitively block ACh at the nicotinic receptors (Figure 3). That is, they compete with ACh at the receptor without stimulating it, thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction.

Their competitive action can be **overcome** by administration of cholinesterase inhibitors, such as neostigmine and edrophonium, which increase the concentration of ACh in the neuromuscular junction. Anesthesiologists employ this strategy to shorten the duration of the neuromuscular blockade. **In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.**

b. At high doses:

Nondepolarizing agents can block the ion channels of the motor endplate. This leads to **further weakening of neuromuscular transmission**, thereby reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers.
With **complete blockade**, the muscle does not respond to direct electrical stimulation.

2. Actions:

Muscles have differing sensitivity to blockade by competitive agents. Small, rapidly contracting muscles of the **face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles**. Next, **the intercostal muscles are affected and, lastly, the diaphragm**.

The **muscles recover in the reverse manner**.

[Note: **Sugammadex** is a selective relaxant binding agent that terminates the action of both rocuronium and vecuronium and can be used to speed recovery

3. Pharmacokinetics:

All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or **more quaternary amines in their bulky ring structure that prevent absorption from the gut.**

They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Drug action is terminated in a variety of ways.

Pancuronium is excreted **unchanged** in urine.

Cisatracurium undergoes organ-independent metabolism (via **Hofmann elimination**) to laudanosine, which is further metabolized and renally excreted.

The amino steroid drugs vecuronium and rocuronium are **deacetylated in the liver and excreted unchanged in bile**.

Mivacurium is eliminated by plasma cholinesterase.

The choice of agent depends on the desired onset and duration of muscle relaxation and the route of elimination.

Drug interactions:

a. Cholinesterase inhibitors:

Drugs such as neostigmine, physostigmine, pyridostigmine, and edrophonium can overcome the action of nondepolarizing neuromuscular blockers. However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane.
If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

b. Halogenated hydrocarbon anesthetics:

Drugs such as desflurane act to enhance neuromuscular blockade by exerting a **stabilizing action at the NMJ.** These agents sensitize the NMJ to the effects of neuromuscular blockers.

c. Aminoglycoside antibiotics:

Drugs such as gentamicin and tobramycin inhibit Ach release from cholinergic nerves by competing with calcium ions. They synergize with pancuronium and other competitive blockers, enhancing the blockade.

d. Calcium channel blockers:

These agents may increase the neuromuscular blockade of competitive blockers.

B. Depolarizing agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers. **Succinylcholine is the only depolarizing muscle relaxant in use today.**

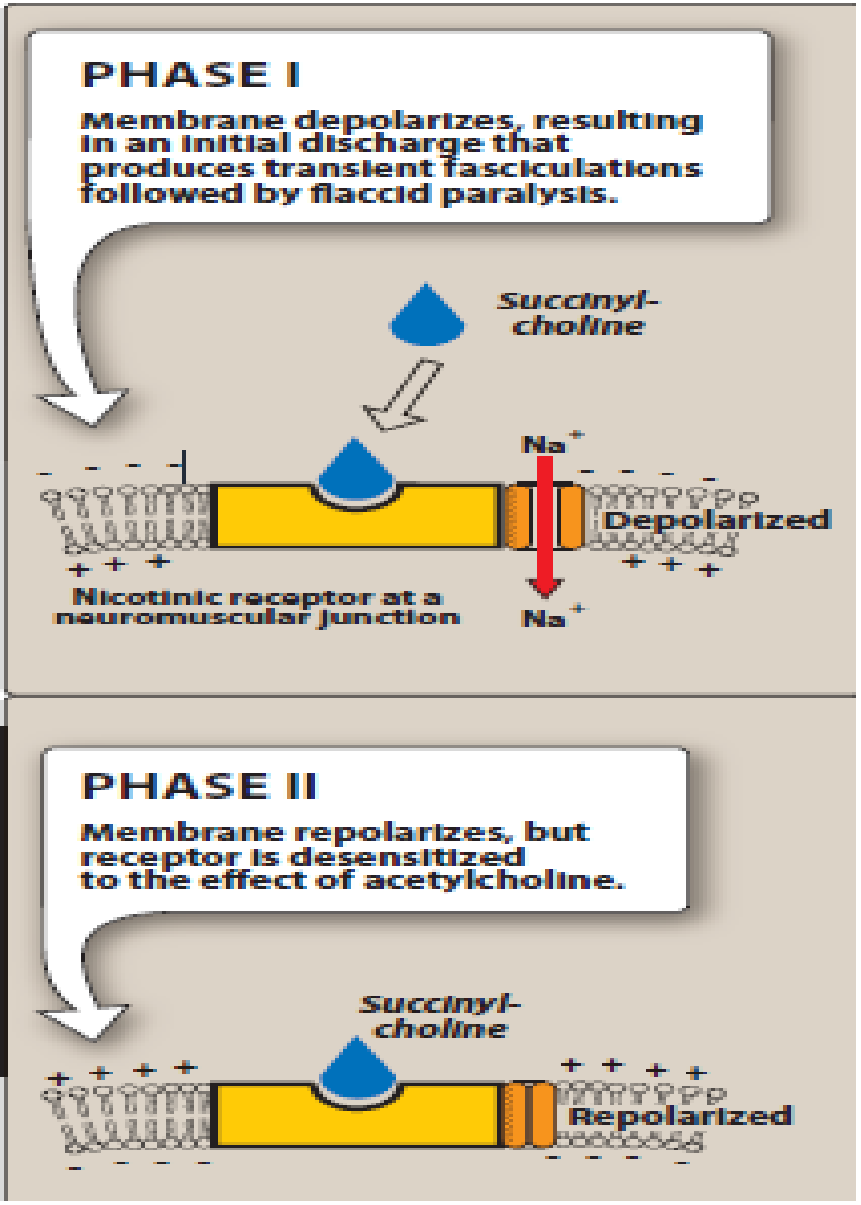


Figure 4: Mechanism of action of depolarizing neuromuscular blocking drugs.

1. Mechanism of action:

Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 4). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor.

The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations).

Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.

2. Actions:

As with the competitive blockers, the respiratory muscles are paralyzed last.

Succinylcholine initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing neuromuscular blocker prior to succinylcholine.

Normally, the duration of action of succinylcholine is extremely short, due to rapid hydrolysis by plasma pseudocholinesterase.

However, succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).

3. Therapeutic uses:

Because of its rapid onset of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia. **It is also used during electroconvulsive shock treatment.**

4. Pharmacokinetics:

Succinylcholine is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma **pseudocholinesterase**. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation.

5. Adverse effects:

a. Hyperthermia:

Succinylcholine can potentially induce malignant hyperthermia in susceptible patients.

b. Apnea:

Administration of succinylcholine to a patient who is **deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.**
The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances who receive this drug. In patients with electrolyte imbalances who are also receiving digoxin or diuretics (such as heart failure patients) succinylcholine should be used cautiously or not at all.

c. Hyperkalemia:

Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost or in patients with renal failure.