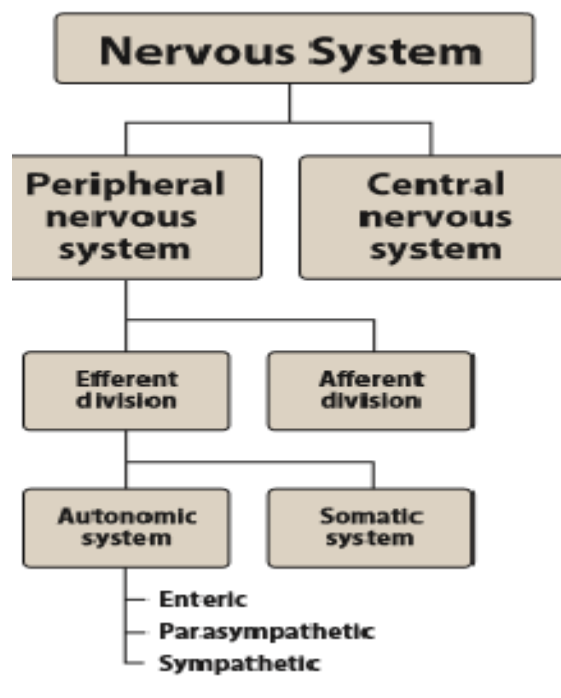


Unit 2 Drug Affecting the Autonomic Nervous System

Chapter 1 The Autonomic nervous system

Introduction to the Nervous System

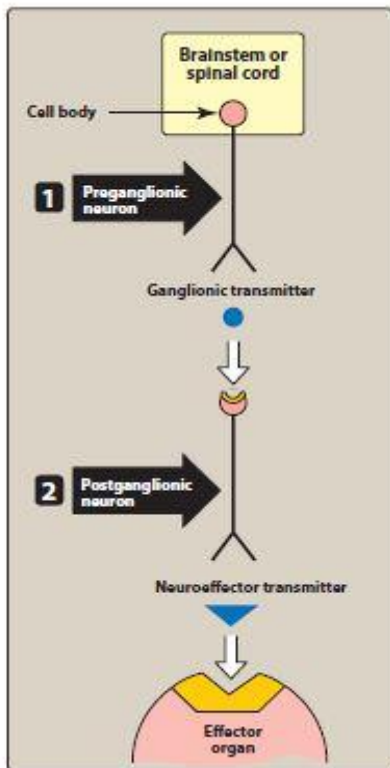
The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS. The peripheral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



Anatomy of ANS

1. Efferent neurons

The ANS carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons: the preganglionic neurons and the postganglionic neurons.



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. 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 smooth muscles of the viscera, cardiac muscle, and the exocrine glands

2. **Afferent neurons:**

Afferent neurons are sensory neurons that carry nerve impulses from sensory stimuli towards the central nervous system and brain.

3. **Sympathetic neurons:**

The efferent ANS is divided into the sympathetic, parasympathetic nervous systems and 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 of the spinal cord. 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. *(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) *

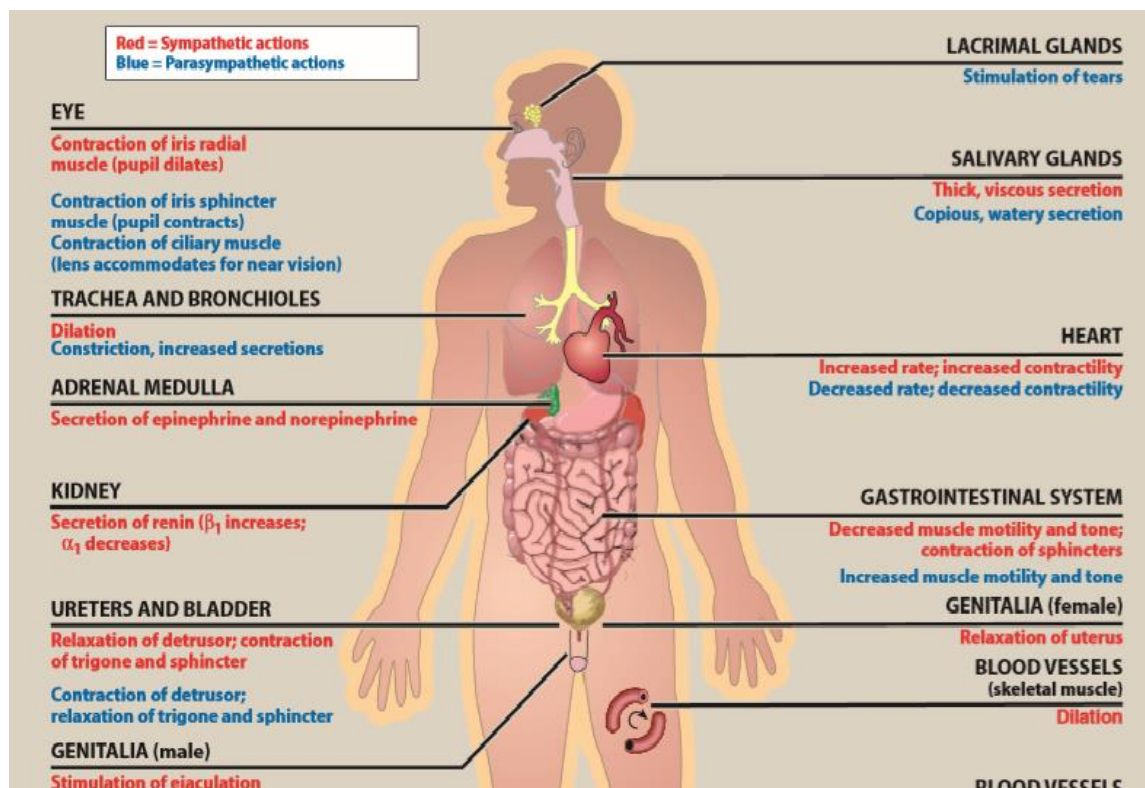
4. Parasympathetic neurons

The parasympathetic preganglionic fibers arise from cranial nerves, as well as from the sacral region* (the sacral region (sacrum) is at the bottom of the spine and lies between the fifth segment of the lumbar spine) * of the spinal cord and synapse in ganglia near or on the effector organs.* (The vagus nerve accounts for 90% of preganglionic parasympathetic fibers in the body)

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.

Actions of sympathetic and parasympathetic nervous systems on effector organs.



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 Ca^{2+} 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.

b. Norepinephrine and epinephrine:

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

AUTONOMIC DRUGS

There are several drugs affecting the autonomic nervous system which, for a better understanding of specific drugs, are classified into groups.

1. Drugs acting on the sympathetic nervous system

- a) Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.
- b) Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2. Drugs acting on the parasympathetic nervous system

- a) Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.
- b) Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.



Chapter 2 Cholinergic agonist (Parasympathomimetics)

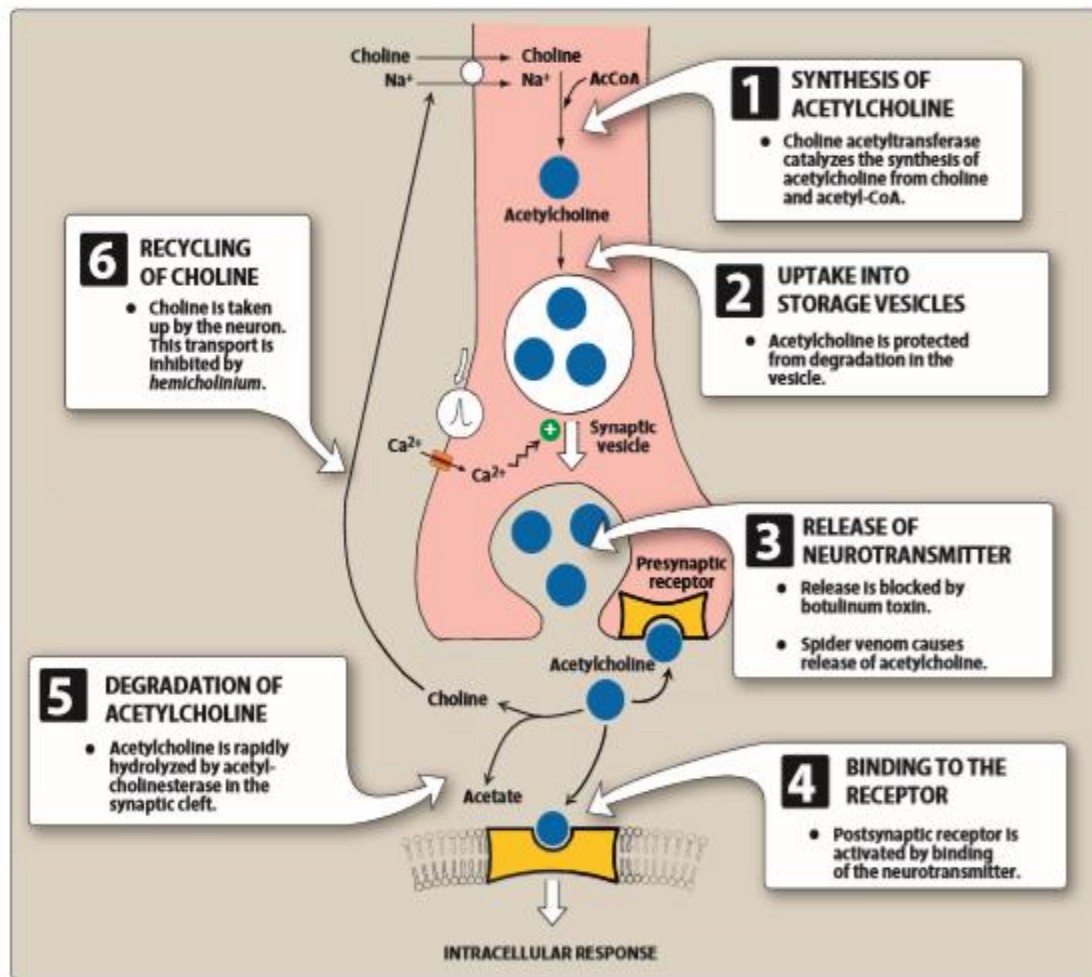
Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine.

DIRECT ACTING	
Acetylcholine	MIOCHOL-E
Bethanechol	URECHOLINE
Carbachol	MIOSTAT, ISOPTO CARBACHOL
Cevimeline	EVOXAC
Nicotine	NICORETTE
Pilocarpine	SALAGEN, ISOPTO CARPINE
INDIRECT ACTING (reversible)	
Ambenonium	MYTELASE
Donepezil	AIRCEPT
Edrophonium	ENLON
Galantamine	RAZADYNE
Neostigmine	PROSTIGMIN
Physostigmine	ANTILIRIUM
Pyridostigmine	MESTINON
Rivastigmine	EXELON
INDIRECT ACTING (irreversible)	
Echothiophate	PHOSPHOLINE IODIDE
REACTIVATION OF ACETYLCHOLINESTERASE	
Pralidoxime	PROTOPAM

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
- 6) recycling of choline and acetate



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

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 ganglia of the peripheral nervous system and 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

[Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration, they may show some activity at nicotinic receptors.]

2. 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.

[Note: At present, no clinically important agents interact solely with the M4 and M5 receptors.

B. Nicotinic receptors

Nicotinic receptors are polypeptides that respond to the neurotransmitter acetylcholine. 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. 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 in skeletal muscles.

Direct acting Cholinergic agonist

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

- a) Esters of choline: methacholine, carbachol, betanecol
- b) Cholinergic alkaloids: pilocarpine, muscarine, arecoline, nicotine

- **Acetylcholine**

ACETYLCHOLINE is the prototypical cholinergic agent. It functions as a neurotransmitter at all cholinergic sites in the body. It lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases.

The actions of acetylcholine may be divided into two main groups: -

1. Nicotinic actions- those produced by stimulation of all autonomic ganglia and the neuromuscular junction
2. Muscarinic actions- those produced at postganglionic cholinergic nerve endings.

Pharmacokinetics

Acetylcholine is poorly absorbed from the gastric mucosa therefore it is ineffective if given orally. The recommended way of administration is parenteral.

In the blood it is rapidly hydrolyzed by the enzyme cholinesterase into acetic acid and choline; this makes its duration of action very short and unreliable for therapeutic purposes.

Pharmacodynamics

- Cardiovascular system
 - Heart → slow heart rate
 - Blood vessels → vasodilator
 - Blood pressure → falls because of the effect on the heart and blood vessels
- Gastrointestinal tract
 - It stimulates the tone and motility of the GI tract but the sphincters will be relaxed.
- Urinary tract
 - It stimulates the detrusor muscle and relaxes the internal urethral sphincter resulting in evacuation of bladder.
- Bronchioles
 - It increases bronchial secretion and brings about bronchoconstriction
- Exocrine gland
 - it stimulates salivary, gastric, bronchial, lachrymal and sweat gland secretions.

- **Bethanechol**

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.

Therapeutic applications:

In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. Bethanechol may also be used to treat neurogenic atony as well as megacolon.

Adverse effect

These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

In direct acting cholinergic agonist (reversible)

- **Physostigmine**

Actions:

Physostigmine has a wide range of effects as a result of its action and stimulates not only the muscarinic and nicotinic sites of the ANS but also the nicotinic receptors of the NMJ. 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.

Therapeutic uses:

The drug increases intestinal and bladder motility. Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine.

Adverse effect

The effects of physostigmine on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.



Chapter 3 Cholinergic Antagonists

Cholinergic antagonist is a general term for agents that bind to cholinergic receptors (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, antimuscarinic agents or parasympatholytics.

ANTIMUSCARINIC AGENTS	
<i>Atropine</i>	ISOPTO ATROPINE
<i>Benztropine</i>	COGENTIN
<i>Cyclopentolate</i>	AK-PENTOLATE, CYCLOGYL
<i>Darifenacin</i>	ENABLEX
<i>Fesoterodine</i>	TOVIAZ
<i>Ipratropium</i>	ATROVENT
<i>Oxybutynin</i>	DITROPAN, GELNIQUE, OXYTROL
<i>Scopolamine</i>	ISOPTO HYOSCINE, TRANSDERM SCOP
<i>Solifenacin</i>	VESICARE
<i>Tiotropium</i>	SPIRIVA HANDIHALER
<i>Tolterodine</i>	DETROL
<i>Trihexyphenidyl</i>	ARTANE
<i>Tropicamide</i>	MYDRIACYL, TROPICACYL
<i>Tropium chloride</i>	SANCTURA
GANGLIONIC BLOCKERS	
<i>Nicotine</i>	NICODERM, NICORETTE, NICOTROL INHALER
NEUROMUSCULAR BLOCKERS	
<i>Cisatracurium</i>	NIMBEX
<i>Pancuronium</i>	PAVULON
<i>Rocuronium</i>	ZEMURON
<i>Succinylcholine</i>	ANECTINE, QUELICIN
<i>Vecuronium</i>	ONLY GENERIC

- **Antimuscarinic Agents**

These agents 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 do not 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. [Note: A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.]

➤ **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.

Actions

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.

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.

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

Secretions: Atropine blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to atropine.

Therapeutic uses:

Ophthalmic: Topical atropine exerts both mydriatic and cycloplegic effects. Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed.

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

Cardiovascular: The drug is used to treat bradycardia of varying etiologies.

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

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). The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

Pharmacokinetics

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

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 that it may elicit.



Chapter 4

Adrenergic Agonist

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Adrenergic drugs that activate adrenergic receptors are termed sympathomimetics.

DIRECT-ACTING AGENTS	
<i>Albuterol</i>	ACCUNE ^B , PROAIR HFA, VENTOLIN HFA
<i>Clonidine</i>	CATAPRES, DURACLON
<i>Dobutamine</i> *	DOBUTREX
<i>Dopamine</i> *	
<i>Epinephrine</i> *	ADRENALIN, EPIPEN
<i>Fenoldopam</i>	CORLOPAM
<i>Formoterol</i>	FORADIL AEROLIZER, PERFORMIST
<i>Isoproterenol</i> *	ISUPREL
<i>Mirabegron</i>	MYRBETRIQ
<i>Norepinephrine</i> *	LEVOPHED
<i>Phenylephrine</i>	NEO-SYNEPHRINE, SUDAFED PE
<i>Salmeterol</i>	SEREVENT DISKUS
<i>Terbutaline</i>	
INDIRECT-ACTING AGENTS	
<i>Amphetamine</i>	ADDERALL
<i>Cocaine</i>	
DIRECT AND INDIRECT ACTING (mixed action) AGENTS	
<i>Ephedrine</i>	VARIOUS
<i>Pseudoephedrine</i>	SUDAFED

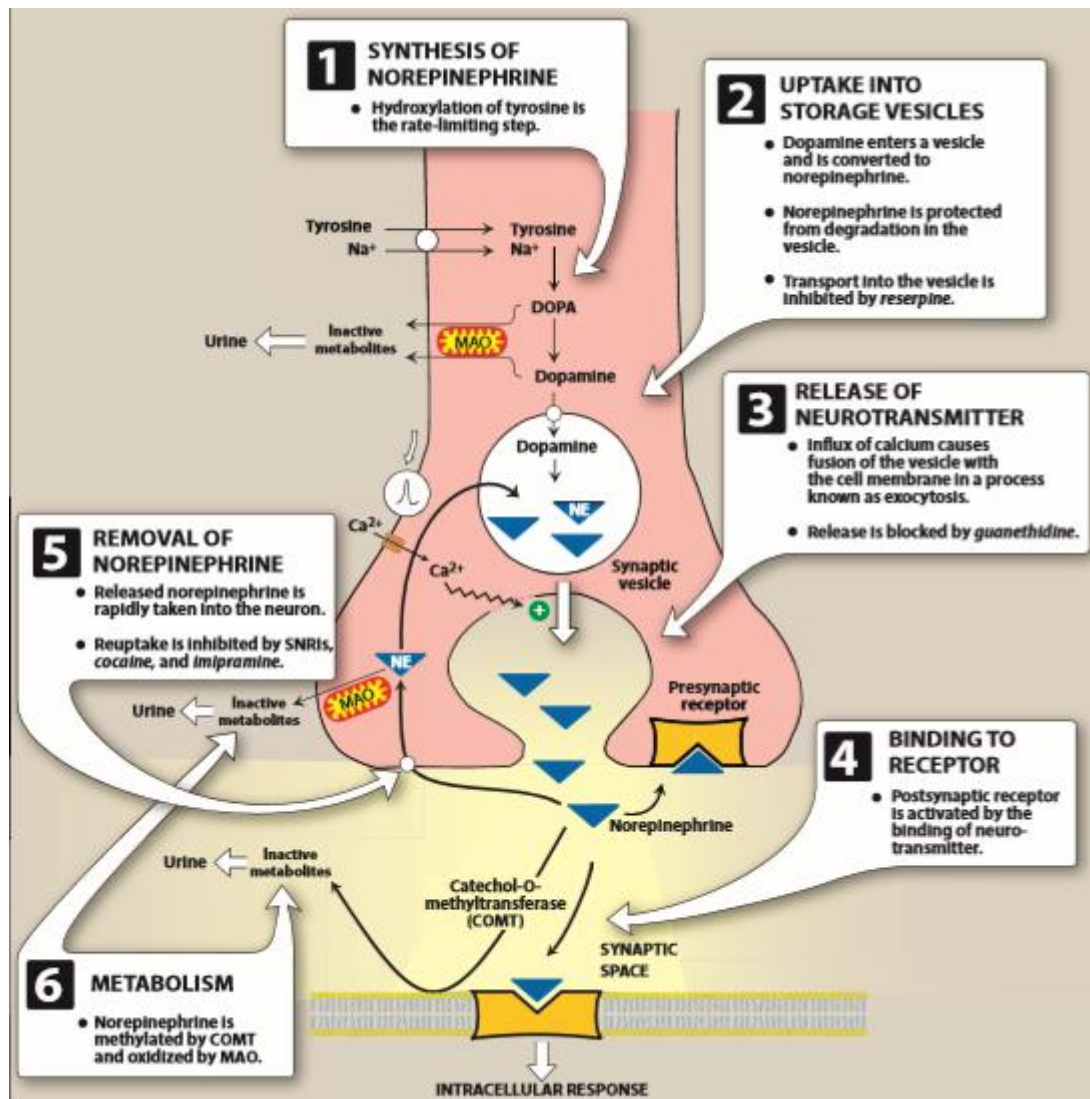
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THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ.

Neurotransmission at adrenergic neurons

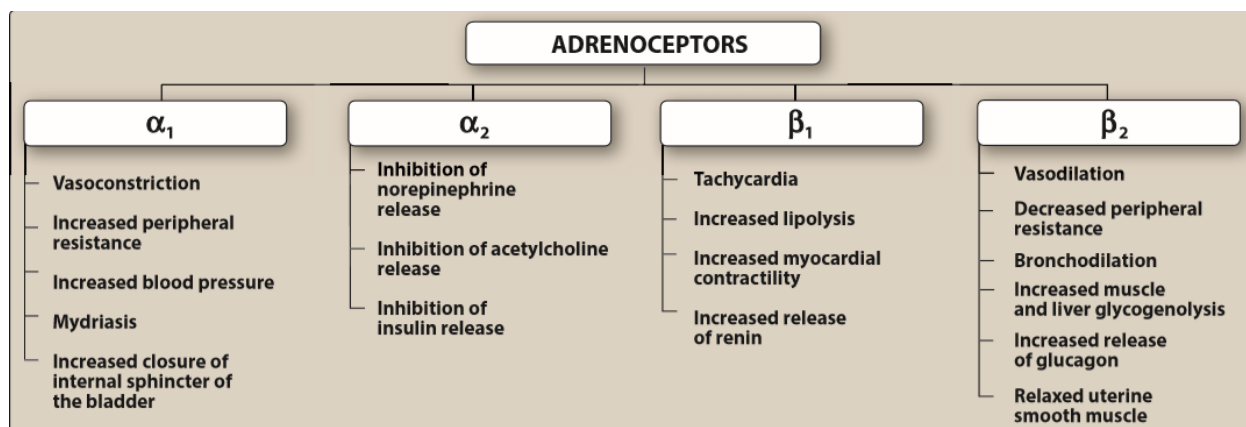
Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.



Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β , are classified on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol. Each of these main receptor types has a number of specific receptor subtypes that have been identified.

Major effects mediated by α - and β -adrenoceptors.



CHARACTERISTICS OF ADRENERGIC AGONISTS

Most of the adrenergic drugs are derivatives of β -phenylethylamine. Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are

- 1) The number and location of OH substitutions on the benzene ring and
- 2) The nature of the substituent on the amino nitrogen

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines. These compounds share the following properties:

1. High potency
2. Rapid inactivation
3. Poor penetration into the CNS.

C. Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include phenylephrine, ephedrine, and amphetamine. These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Mechanism of action of adrenergic agonists

1. Direct-acting agonists

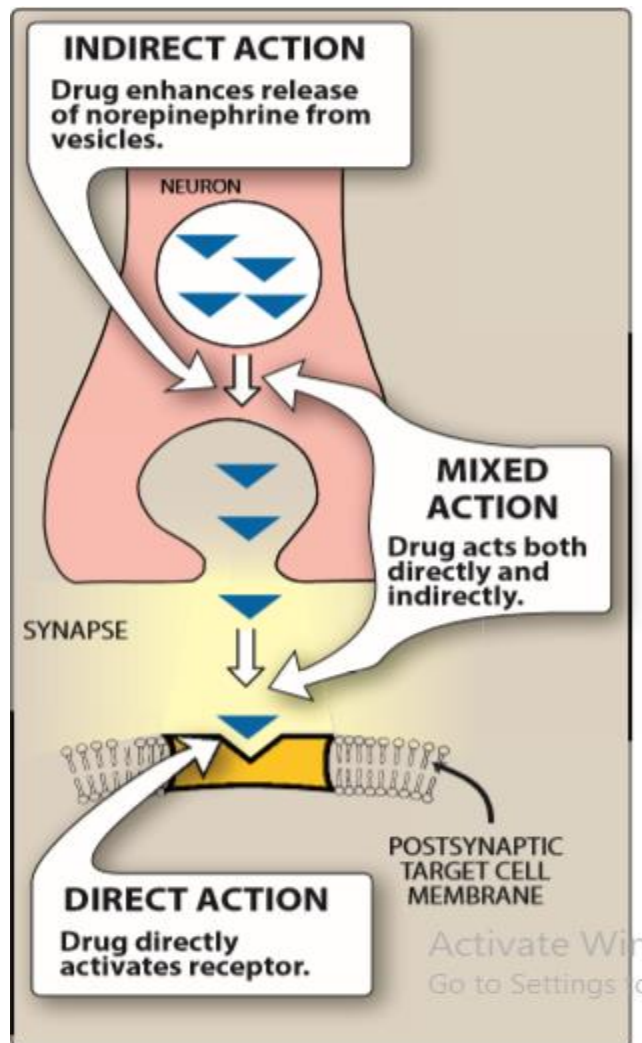
These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla. Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, and phenylephrine.

2. Indirect-acting agonists:

These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron. The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include cocaine and amphetamines, respectively.

3. Mixed-action agonists

Ephedrine and its stereoisomer, pseudoephedrine, both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron.



Direct-Acting Adrenergic Agonist

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

A. Epinephrine

Epinephrine is one of the four catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells along with norepinephrine. On stimulation, the adrenal medulla releases about 80% epinephrine and 20% norepinephrine directly into the circulation. Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

Actions

Cardiovascular: The major actions of epinephrine are on the cardiovascular system. Epinephrine strengthens the contractility of the myocardium and increases its rate of contraction. Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. Epinephrine activates β_1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β_2 effects). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β_2 receptor-mediated vasodilation in the skeletal muscle vascular bed.

Respiratory Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.

Hyperglycemia: Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2 effect), increased release of glucagon (β_2 effect), and a decreased release of insulin (α_2 effect).

Lipolysis

Epinephrine initiates lipolysis through agonist activity on the β receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

Therapeutic uses

- a. **Bronchospasm** Epinephrine is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice and can be lifesaving in this setting.
- b. **Anaphylactic shock:**s Epinephrine is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.
- c. **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.
- d. **Anesthetics:** Local anesthetic solutions may contain low concentrations of epinephrine. Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection.

Pharmacokinetics

Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route is intramuscular (anterior thigh) due to rapid absorption. In emergency situations, epinephrine is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, and by inhalation.

Adverse effects

Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin. Epinephrine can also induce pulmonary edema. Epinephrine may have enhanced cardiovascular actions in patients with hyperthyroidism, and the dose must be reduced in these individuals.



Chapter 5 Adrenergic Antagonists

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines.

α BLOCKERS

Alfuzosin UROXATRAL
Doxazosin CARDURA
Phenoxybenzamine DIBENZYLINE
Phentolamine REGITINE
Prazosin MINIPRESS
Tamsulosin FLOMAX
Terazosin HYTRIN
Yohimbine YOCON

β BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol BETOPTIC-S, KERLONE
Bisoprolol ZEBETA
Carteolol CARTROL
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol Inderal LA, INNOPRAN XL
Timolol BETIMOL, ISTALOL, TIMOPTIC

DRUGS AFFECTING NEURO-TRANSMITTER UPTAKE OR RELEASE

Reserpine SERPASIL

➤ **Alpha blockers**

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α -adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given.

• **Phenoxybenzamine**

Phenoxybenzamine is nonselective, linking covalently to both α_1 and α_2 receptors. The block is irreversible and noncompetitive, and the only way the body can overcome the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of phenoxybenzamine last about 24 hours. After the drug is injected, a delay of a few hours occurs before a blockade develops.

Actions

Cardiovascular effects

By blocking α receptors, phenoxybenzamine prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic inhibitory α_2 receptors in the heart can contribute to an increased cardiac output. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

Epinephrine reversal

All α -adrenergic blockers reverse the α agonist actions of epinephrine. For example, the vasoconstrictive action of epinephrine is interrupted, but vasodilation of other vascular beds caused by stimulation of β_2 receptors is not blocked. Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine.

Therapeutic uses

Phenoxybenzamine is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. It may be used prior to surgical removal of the tumor to prevent a hypertensive crisis, and it is also useful in the chronic management of inoperable tumors. Phenoxybenzamine is sometimes effective in treating Raynaud disease and frostbite.

Adverse effect

Phenoxybenzamine can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. Phenoxybenzamine should be used with caution in patients with cerebrovascular or cardiovascular disease.

➤ **B-Adrenergic Blocking Agent**

All of the clinically available β -blockers are competitive antagonists. Nonselective β -blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors. Although all β -blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β -Blockers are effective in treating hypertension, angina, cardiac arrhythmias, myocardial infarction,

heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches.

- **Propranolol: A nonselective β antagonist**

Propranolol is the prototype β -adrenergic antagonist and blocks both β_1 and β_2 receptors with equal affinity. Sustained-release preparations for once-a-day dosing are available.

Actions

a. Cardiovascular

Propranolol diminishes cardiac output, having both negative inotropic and chronotropic effects. It directly depresses sinoatrial and atrioventricular nodal activity. The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β -blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β_1 receptors, and these effects are useful in the treatment of angina. The β -blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias.

b. Peripheral vasoconstriction

Nonselective blockade of β receptors prevents β_2 -mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance. The reduction in cardiac output produced by all β -blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of propranolol. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

c. Bronchoconstriction:

Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle. This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β -blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Disturbances in glucose metabolism:

β blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if propranolol is given to a diabetic patient receiving insulin, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection. β -blockers also attenuate the normal physiologic response to hypoglycemia.

e. Blocked action of isoproterenol

Nonselective β -blockers, including propranolol, have the ability to block the actions of isoproterenol (β_1 , β_2 agonist) on the cardiovascular system. Thus, in the presence of a β -blocker, isoproterenol does not produce cardiac stimulation. The actions of norepinephrine on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.

Therapeutic uses

Hypertension: Propranolol does not reduce blood pressure in people with normal blood pressure. Propranolol lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release

from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects.

Angina pectoris: Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. Propranolol is, thus, useful in the chronic management of stable angina.

Myocardial infarction: Propranolol and other β -blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β -blockers.

Migraine: Propranolol is effective in reducing migraine episodes when used prophylactically. It is one of the more useful β -blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS.

Hyperthyroidism: Propranolol and other β -blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β -blockers may be lifesaving in protecting against serious cardiac arrhythmias.

Pharmacokinetics

After oral administration, propranolol is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation. The volume of distribution of propranolol is quite large, and the drug readily crosses the blood–brain barrier due to its high lipophilicity. Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

Adverse effects:

Bronchoconstriction: Propranolol has the potential to cause significant bronchoconstriction due to blockade of β_2 receptors. Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, propranolol is contraindicated in patients with COPD or asthma.

Arrhythmias: Treatment with β -blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β -blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

Sexual impairment: Because ejaculation in the male is mediated through α -adrenergic activation, β -blockers do not affect ejaculation or internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β receptor blockade.

Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β -blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β -

blockers. A major role of β receptors is to mobilize energy molecules such as free fatty acids. Patients administered nonselective β -blockers have increased low-density lipoprotein (“bad” cholesterol), increased triglycerides, and reduced high-density lipoprotein (“good” cholesterol). These effects on the serum lipid profile may be less pronounced with the use of β_1 -selective antagonists such as metoprolol.

CNS effects; Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with more hydrophilic β -blockers (for example, atenolol), since they do not cross the blood–brain barrier as readily.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
<i>Propranolol</i>	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
<i>Nadolol</i> <i>Pindolol</i> ¹	β_1, β_2	Hypertension
<i>Timolol</i>	β_1, β_2	Glaucoma, hypertension
<i>Atenolol</i> <i>Bisoprolol</i> ² <i>Esmolol</i> <i>Metoprolol</i> ²	β_1	Hypertension Angina Myocardial infarction
<i>Acebutolol</i> ¹	β_1	Hypertension
<i>Nebivolol</i>	$\beta_1, \text{NO} \uparrow$	Hypertension
<i>Carvedilol</i> ² <i>Labetalol</i>	$\alpha_1, \beta_1, \beta_2$	Hypertension