Pharmacology

Lec. 5+6 College of dentistry
Dr Maha Mohsin Khalaf University of Baghdad

ADRENERGIC AGONISTS

The sympathetic nervous system is an important regulator of virtually all organ systems. This is particularly evident in the regulation of blood pressure. The autonomic nervous system is crucial for the maintenance of blood pressure even under relatively minor situations of stress (eg, the gravitational stress of standing). The ultimate effects of sympathetic stimulation are mediated by release of norepinephrine from nerve terminals, which then activates adrenoceptors on postsynaptic sites. Also, in response to a variety of stimuli such as stress, the adrenal medulla releases epinephrine, which is transported in the blood to target tissues. The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block activation of adrenergic receptors are termed sympatholytics.
The sympathomimetics constitute a very important group of drugs used for cardiovascular, respiratory, and other conditions. They are readily divided into subgroups on the basis of their spectrum of action (α-, β-, or dopamine-receptor affinity) or mode of action (direct or indirect) (figure 1)

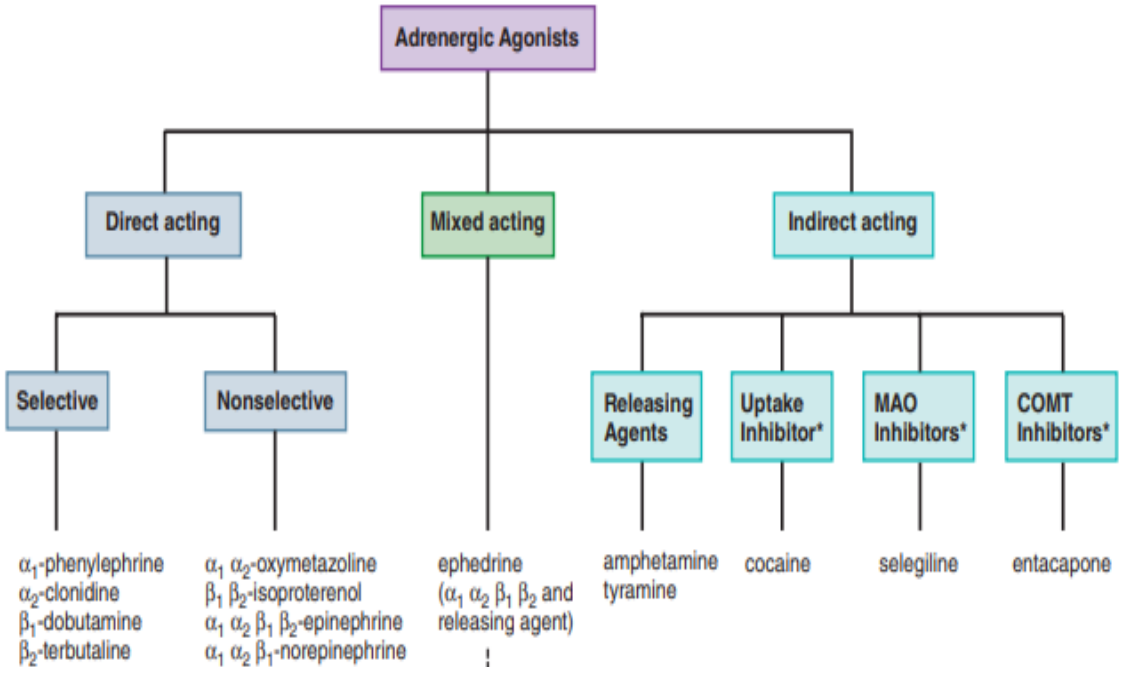


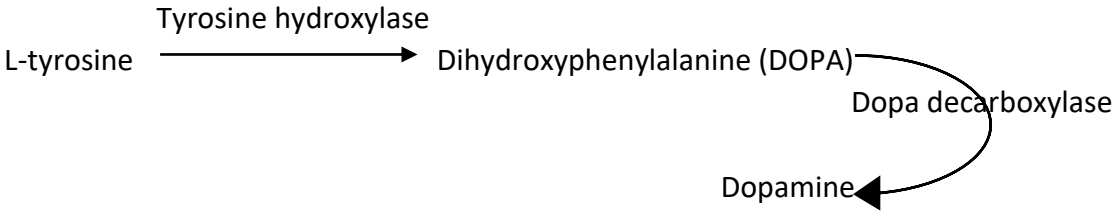
Figure 1: adrenergic agonists classification

- ### Neurotransmission at adrenergic neurons:

Neurotransmission at adrenergic neurons is similar to what was describe in cholinergic neurons, except that norepinephrine (noradrenaline) is the neurotransmitter instead of acetylcholine.

The neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.

- **Synthesis of norepinephrine (figure 2)**
  The metabolic precursor for norepinephrine (noradrenaline) is L-tyrosine, which is transported by a Na^+ linked carrier into adrenergic neurons. **Tyrosine hydroxylase**, a cytosolic enzyme that catalyses the conversion of tyrosine to dihydroxyphenylalanine (dopa). This first hydroxylation step is the main control point for noradrenaline synthesis. Tyrosine hydroxylase is inhibited by the end product of the biosynthetic pathway, noradrenaline.
  The next step, conversion of dopa to dopamine, is catalysed by **dopa decarboxylase** in the presynaptic neuron.



- **Storage of norepinephrine in vesicles**
  Dopamine is then transported into synaptic vesicles by an amine transporter system. Dopamine is next hydroxylated to form norepinephrine by the enzyme **dopamine β-hydroxylase**.
  In the adrenal medulla, norepinephrine is methylated to form epinephrine (adrenaline), 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.

- **Release of norepinephrine**: An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse.

- **Binding to receptors**: Norepinephrine released binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors results in the formation of intracellular second messengers (the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle) to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α2 subtype) that modulate the release of the neurotransmitter.
- **Removal of norepinephrine**:
  Norepinephrine may 1) diffuse out of the synaptic space and enter the systemic circulation; 2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the

synaptic space; or 3) undergo reuptake back into the neuron. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

- **Potential fates of recaptured norepinephrine**: Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

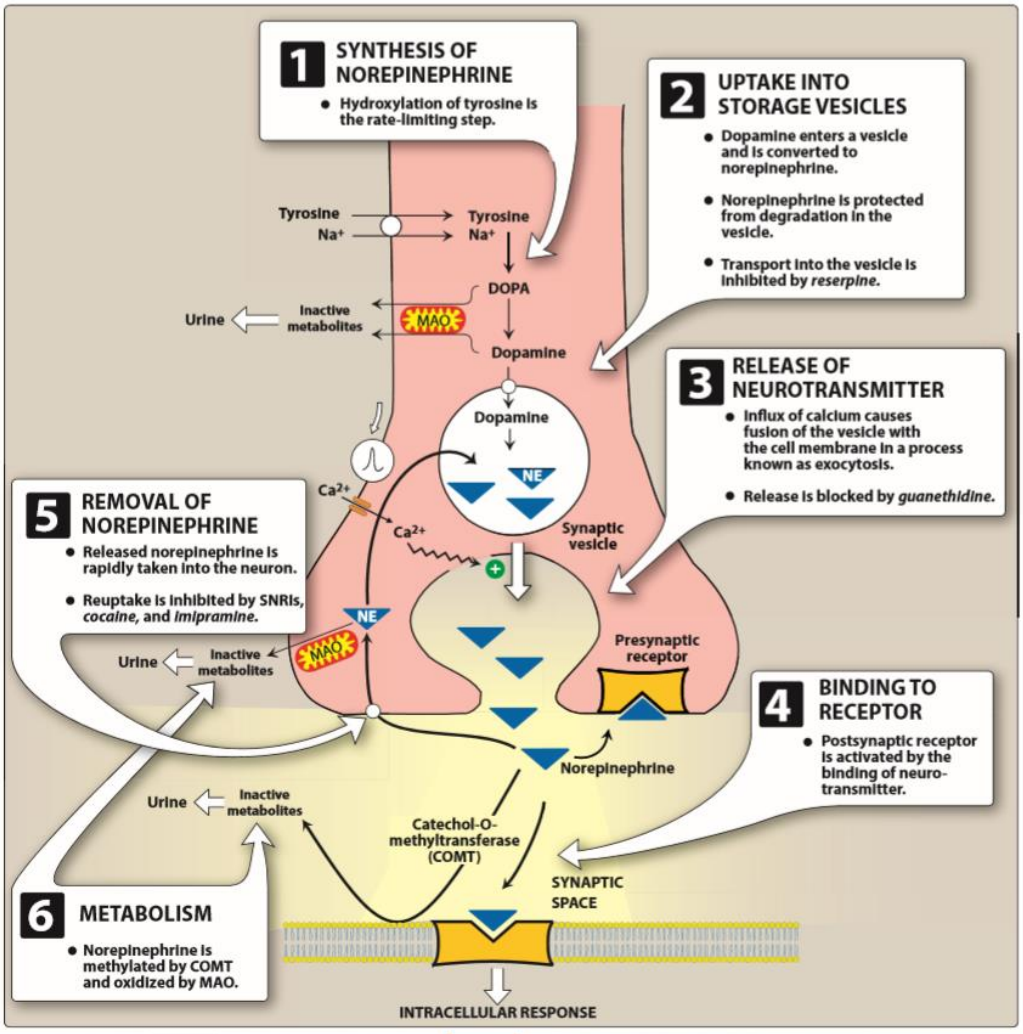


Figure 2: norepinephrine synthesis

Adrenergic receptors:

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically (figure 3). Two main families of receptors, designated α and β, are classified based on response to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.

α-Adrenoceptors

For α receptors, the rank order of potency and affinity is epinephrine ≥ norepinephrine >> isoproterenol. The α-adrenoceptors are divided into two subtypes, α1 and α2, based on their

affinities for α agonists and antagonists. For example, α1 receptors have a higher affinity for phenylephrine than α2 receptors.

α1 Receptors These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α1 receptors results in the generation of second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).

α2 Receptors These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine (inhibit). This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. The effects of binding at α2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

β-Adrenoceptors: For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β1, β2, and β3, based on their affinities for adrenergic agonists and antagonists. β1 receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β2 receptors have a higher affinity for epinephrine than for norepinephrine. Thus, tissues with a predominance of β2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.

Dopamine Receptors: The D 1 receptor is typically associated with the stimulation of adenylyl cyclase for example, D 1 -receptor–induced smooth muscle relaxation is presumably due to cAMP accumulation in the smooth muscle of those vascular beds in which dopamine is a vasodilator. D 2 receptors have been found to inhibit adenylyl cyclase activity, open potassium channels, and decrease calcium influx.

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

Figure 3: adrenergic receptors

- **Desensitization of receptors:**

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and 3) an inability to couple to G-protein, because the receptor has been phosphorylated on the cytoplasmic side.

- **Characteristic of adrenergic agonists (catecholamine and non):**

Most 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.

Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain. Pharmacologically, the most important ones are: noradrenaline (norepinephrine), adrenaline (epinephrine), dopamine, and isoprenaline (also known as isoproterenol).

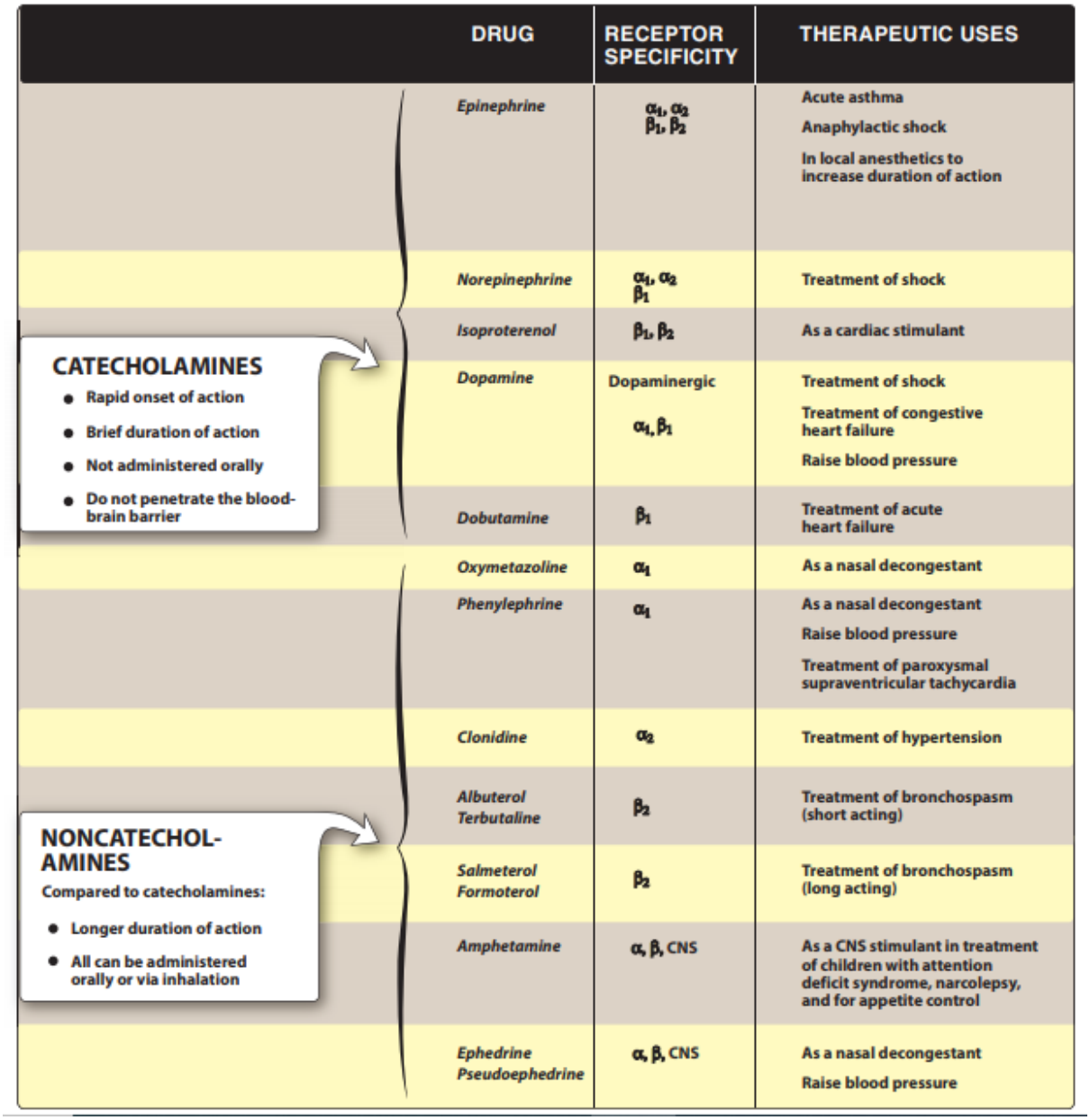
These compounds share the following properties:

1. **High potency**: Catecholamines show the highest potency in directly activating α or β receptors.
2. **Rapid inactivation**: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.
3. **Poor penetration into the CNS**: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

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.

Adrenergic agonists classification (figure 4)

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, dopamine, and phenylephrine.
2. Indirect-acting agonists These agents may block the reuptake of norepinephrine (cocaine)or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (amphetamine). The norepinephrine then binds to α or β receptors.
3. Mixed-action agonists Ephedrine and its stereoisomer, pseudoephedrine, both stimulate adrenoceptors directly and enhance release of norepinephrine from the adrenergic neuron.



DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure
Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

Figure 4: adrenergic agonist classification

Direct-acting agonists

Direct-acting agonist: 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 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.

1. Actions:

a. Cardiovascular: increase contractility of the myocardium (positive inotrope: β1 action) and increases its rate of contraction (positive chronotrope: β1 action). Therefore, cardiac output

increases. Epinephrine activates β1 receptors on the kidney to cause renin release (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 (β2 effects).
Renal blood flow is decreased. The cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β2 receptor–mediated vasodilation in the skeletal muscle vascular bed.
b. Respiratory: Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.
c. Hyperglycemia: Epinephrine increases glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).
d. Lipolysis: Epinephrine initiates lipolysis through β receptors of adipose tissue.

2. Therapeutic uses: a. Bronchospasm (acute asthma and anaphylactic shock).
b. Anaphylactic shock: type I hypersensitivity reactions (including anaphylaxis)
c. Cardiac arrest
d. Anesthetics: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts)
3. Pharmacokinetics: Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation). It can be given IV , IM, and by inhalation. It is rapidly metabolized by MAO and COMT.
4. 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, and can lead to myocardial ischemia or infarction (MI). Epinephrine can also induce pulmonary edema.

Norepinephrine

when administered in therapeutic doses, the α-adrenergic receptor is most affected (α1=α2>β1).
1. **Cardiovascular actions:**
a. **Vasoconstriction**: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds (α1 effect). Both systolic and diastolic blood pressures increase.
b. Baroreceptor reflex: Norepinephrine increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug. When atropine, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia.

2. Therapeutic uses: Norepinephrine is used to treat shock.
3. Pharmacokinetics: Norepinephrine is given IV. It is rapidly metabolized by MAO and COMT,.
4. Adverse effects: These are similar to epinephrine. In addition, it may cause blanching and sloughing of skin along an injected vein.

C. Isoproterenol:

Isoproterenol is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its action on α receptors is insignificant. Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output. Isoproterenol also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Isoproterenol is a potent bronchodilator (β2 effect). Isoproterenol may be useful in atrioventricular (AV) block.

D. Dopamine:

Dopamine can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation.

1. Actions: a. Cardiovascular: Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects. At very high doses, dopamine activates α1 receptors on the vasculature, resulting in vasoconstriction.

b. Renal and visceral: Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera. Therefore, dopamine is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

2. Therapeutic uses: Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above.

Adverse effects: nausea, hypertension, and arrhythmias.

V. Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors (Amphetamine, tyramine, and cocaine).

Amphetamine: causes release of stored norepinephrine, its main effect is CNS stimulation.
Therapeutic uses: in attention deficit hyperactivity disorder (ADHD), CNS stimulatory effects, suppression of appetite.

Tyramine: inhibit the uptake of norepinephrine, it has been used for weight loss. It is found in fermented foods. Normally it is oxidized by MAO, but if the patient is taking MAO inhibitors, it can precipitate serious vasopressor effect.

Cocaine: Block reuptake of catecholamine at adrenergic nerve terminal. Effect of cocaine on CNS is general stimulation, euphoria, dysphoria, followed by depression. On CVS in small doses it causes bradycardia, and at higher doses tachycardia; vasoconstriction; and myocardial infarction. Cocaine causes local anaesthesia by blocking Na+ channels.

A. MIXED-ACTION AGONISTS, Ephedrine and pseudoephedrine.

Mixed-Action Adrenergic Agonists Ephedrine and pseudoephedrine. They not only enhance release of stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and it is indicated in anesthesia-induced hypotension. Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. Oral pseudoephedrine is primarily used to treat nasal and sinus congestion. Pseudoephedrine has been illegally used to produce methamphetamine.

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. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system (figure 5).

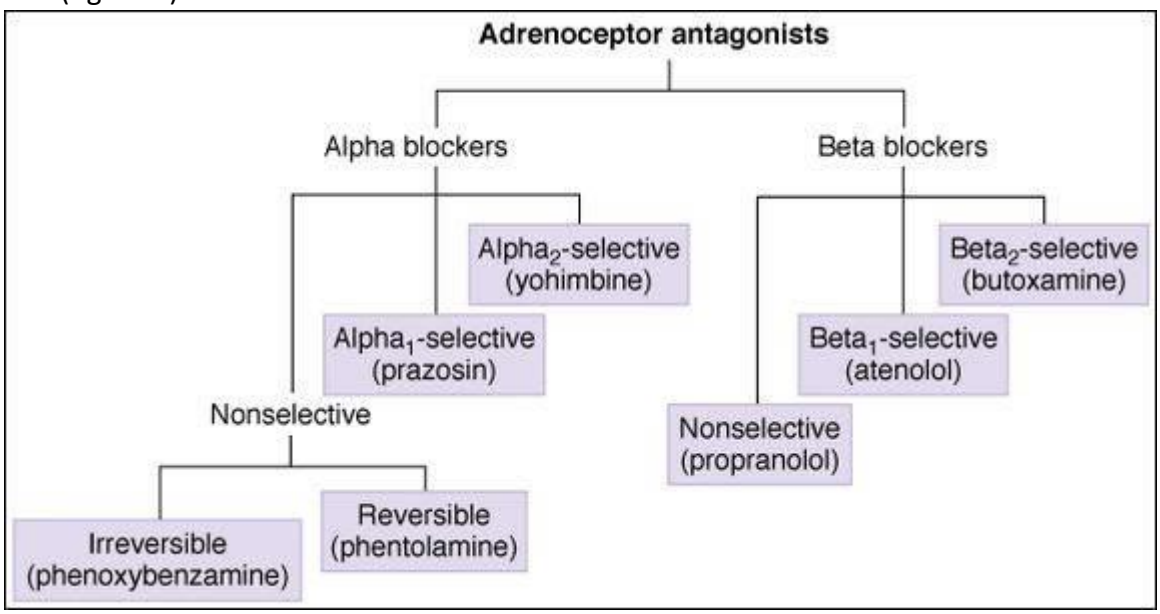


Figure 5: Adrenoceptor antagonists.

α-Adrenergic blocking agents: Phentolamine, Phenoxybenzamine, Prazosin, Terazosin, Doxazocin, Tamsulosin, Alfuzocin, Yohimbine.

1-Non –selective Irreversible, long-acting—Phenoxybenzamine is the prototypical long-acting α blocker; it differs from other adrenoceptor blockers in being irreversible in action. It is slightly α1-selective.

Reversible, shorter-acting—Phentolamine is a competitive, reversible blocking agent that does not distinguish between α1 and α2 receptors.

2-Alpha1-selective—Prazosin is a highly selective, reversible pharmacologic α1 blocker. Doxazosin, terazosin, and tamsulosin are similar drugs.

3-Alpha2-selective—Yohimbine

Clinical Uses:

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:

1. Nonselective α blockers—Nonselective α blockers have limited clinical applications. The best-documented application is in the presurgical management of pheochromocytoma. Such patients may have severe hypertension and reduced blood volume, which should be corrected before subjecting the patient to the stress of surgery. Phenoxybenzamine is usually used during this preparatory phase; phentolamine is sometimes used during surgery.

Phentolamine or yohimbine has been used by direct injection to cause penile erection in men with erectile dysfunction, but phosphodiesterase inhibitors are more popular.
2. Selective α blockers—Prazosin, doxazosin, and terazosin are used in hypertension. These α1 blockers, as well as tamsulosin and silodosin are also used to reduce urinary hesitancy and prevent urinary retention in men with benign prostatic hyperplasia.
3. Yohimbine is a selective competitive α2-blocker. Has been used as a sexual stimulant and in the treatment of erectile dysfunction.

β-ADRENERGIC BLOCKING AGENTS: They can be classified in to:
1. Non-selective β1 and β2 antagonists (e.g. propanolol, Nadalol, Timolol, Pindolol).
2. β1-selective (e.g. Metoprolol, Atenolol,Bisoprlol, Esmolol, Acebutolol, Betaxolol).

3.Non-selective or selective β-blockers with vasodilating effect (due to α1-blocking effect)
Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β1 and β2 receptors, whereas cardio-selective β antagonists primarily block β1 receptors. [Note: There are no clinically useful β2 antagonists.] These drugs also differ in intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics. 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 is the prototype. Drugs in this group are usually classified into subgroups on the basis of β1 selectivity, partial agonist activity, local anesthetic action, and lipid-solubility
1**. Receptor selectivity—**Beta1-receptor selectivity (β1 block > β2 block) is a property of acebutolol, atenolol, esmolol, metoprolol, and several other β blockers. This property may be an advantage when treating patients with asthma because functioning β2 receptors are important in preventing bronchospasm in such patients. Nadolol, propranolol, and timolol are typical
2**. Partial agonist activity**—Partial agonist activity ("intrinsic sympathomimetic activity") may be an advantage in treating patients with asthma because these drugs (eg, pindolol, acebutolol)—at least in theory—are less likely to cause bronchospasm. In contrast, full antagonists such as propranolol are more likely to cause severe bronchospasm in patients with airway disease.
3. Local anesthetic activity—Local anesthetic activity ("membrane-stabilizing activity")

Effects and Clinical Uses

Most of the organ-level effects of β blockers are predictable from blockade of the β-receptor–mediated effects of sympathetic discharge. The clinical applications of β blockade are remarkably broad. The treatment of open angle glaucoma involves the use of several groups of autonomic drugs as well as other agents. The cardiovascular applications of β blockers—especially in hypertension, angina, and arrhythmias—are extremely important. Treatment of

chronic (not acute) heart failure has become an important application of β blockers. Several large clinical trials have shown that some, but not all, β blockers can reduce morbidity and mortality when used

properly in heart failure. Labetalol, carvedilol, and metoprolol have documented benefits in this application. Pheochromocytoma is sometimes treated with combined α- and β-blocking agents (eg, labetalol), especially if the tumor is producing large amounts of epinephrine as well as norepinephrine (figure 6)

DRUG SUMMARY TABLE: Adrenoceptor Blockers

Subclass	Mechanism of Action	Clinical Applications
Nonselective ` blockers		
Phentolamine	Competitive pharmacologic antagonism at α receptors	Pheochromocytoma, antidote to overdose of α agonists
Phenoxybenzamine	Irreversible (covalent) binding to α receptors	Pheochromocytoma, carcinoid, mastocytosis, Raynaud's phenomenon
Alpha$_1$-selective blockers		
Prazosin	Competitive antagonism at α_1 receptors	Hypertension, benign prostatic hyperplasia
Doxazosin, terazosin: like prazosin; longer duration of action (12–24 h)		
Tamsulosin, silodosin: like prazosin, approved only for benign prostatic hyperplasia		
Alpha$_2$-selective blockers		
Yohimbine	Competitive antagonism at α_2 receptors	Obsolete use for erectile dysfunction • research use
Nonselective a blockers		
Propranolol	Competitive block of β receptors, local anesthetic effect	Angina, arrhythmias (treatment and prophylaxis), hypertension, thyrotoxicosis, tremor, stage fright, migraine
Timolol, betaxolol, others: lack local anesthetic action; useful in glaucoma		
Pindolol: partial agonist action; possibly safer in asthma		
Nadolol: like propranolol but longer action (up to 24 h) and less CNS effect		
Beta$_1$-selective blockers		
Atenolol	Competitive block of β_1 receptors	Hypertension, angina, arrhythmias
Esmolol: IV agent for perioperative and thyroid storm arrhythmias, hypertensive emergency		
Metoprolol: like atenolol, oral, shown to reduce mortality in heart failure		
Nebivolol: oral β_1-selective blocker with additional nitric oxide-dependent vasodilating action		
Beta$_2$-selective blockers		
Butoxamine	Competitive block of β_2 receptors	None • research use only —
Alpha + beta blockers		
Labetalol	Four isomers; 2 bind and block both α and β receptors	Hypertension, hypertensive emergencies (IV)
Carvedilol: like labetalol, 2 isomers; shown to reduce mortality in heart failure		

Figure 6: adrenoceptor blocking agents.

Drugs affecting the Cardiovascular system (Antihypertensive--Part-1)

Hypertension (HT) occurs when systolic blood pressure exceeds 130 mm Hg or diastolic blood pressure exceeds 80 mm Hg on at least two occasions. The mean arterial pressure can be calculated from the following equation:

Mean arterial pressure = Cardiac output (CO) X Peripheral resistance (PR)

According to the above equation a decrease in either CO or PR will decrease blood pressure. Conversely, any increase in blood pressures can be traced back to something can increase one of these two variables.

HT is also an important risk factor in the development of chronic kidney disease, heart failure and stroke specifically when the patient is asymptomatic. The incidence of morbidity and mortality significantly decreases when HT is diagnosed early and is properly treated.

HT is classified into four categories for the purpose of treatment management as demonstrated in table 1.

Table 1: Classification of blood pressure.

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

ETIOLOGY OF HYPERTENSION

Although HT may occur secondary to other disease processes, more than 90% of patients have essential HT (HT with no identifiable cause).

The main suggested causes for HT are:

1- Family history of HT
2- The prevalence of HT increases with age but decreases with education and income level.
3- Ethnicity
4- The prevalence of HT increases in persons with diabetes, obesity, or disability status

5- In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to HT.

MECHANISMS FOR CONTROLLINGBLOOD PRESSURE

As mentioned above, arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance. Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms: the baroreflexes and the renin–angiotensin–aldosterone system (RAAS). So, most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

A- Baroreceptors and the sympathetic nervous system

Baroreflexes act by changing the activity of the sympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons to send fewer impulses to cardiovascular centres in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure (figure 1).

B- Renin–angiotensin–aldosterone system

The kidney provides long-term control of blood pressure by altering the **blood volume**. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1-adrenoceptors) by releasing the enzyme renin (figure 1). Low sodium intake and greater sodium loss also increase renin release. Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 (AT_1) receptors.

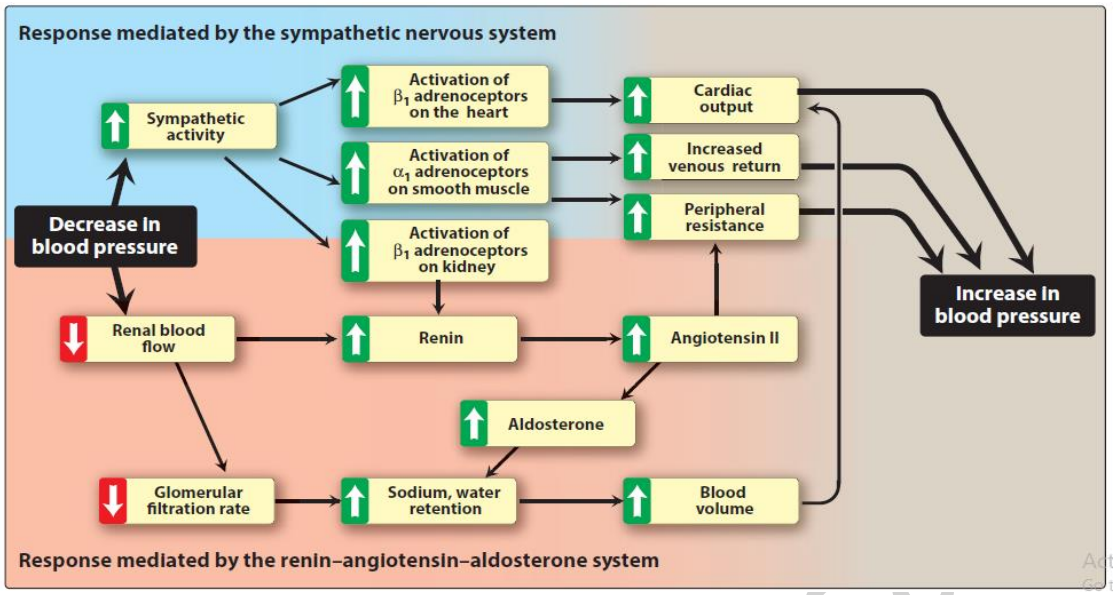


Figure 1: Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

TREATMENT STRATEGIES

- The blood pressure goal when treating HT is **a systolic blood pressure of less than 130 mm Hg and a diastolic blood pressure of less than 80 mm Hg. Mild HT can sometimes be controlled with monotherapy, but most patients require more than one drug to achieve blood pressure control.**
- Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker. If blood pressure is inadequately controlled, a second drug should be added.
- The selection of the 2nd drug is based on minimising the adverse effects of the combined regimen and achieving goal blood pressure.
- Patients with systolic blood pressure greater than 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal should be started on two antihypertensives simultaneously.
- HT treatment plan can be (or should be) individualised. In addition, the blood pressure goals may also be individualised based on concurrent disease states. For instance, in patients with diabetes, some experts recommend a blood pressure goal of less than 140/90 mm Hg.

TYPES OF ANTIHYPERTENSIVE DRUGS:

1- DIURETICS

There are 3 classes of diuretics, which are:

a- Thiazide diuretics

b- Loop diuretics

c- Potassium-sparing diuretics

Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume leading to decrease in blood pressure.

Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure. **Routine serum electrolyte monitoring should be done for all patients receiving diuretics.**

a- Thiazide diuretics:

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone can be used as initial drug therapy for HT unless there are compelling reasons to choose another agent.

Mechanism of action:

Thiazide diuretics lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow (figure 2). **With long-term treatment**, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.

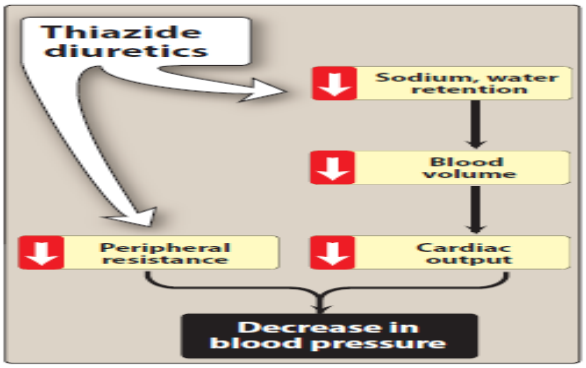


Figure 2: Actions of thiazide diuretics.

Therapeutic uses:

Thiazides are useful in combination therapy with a variety of other antihypertensive agents. With the exception of metolazone, thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m^2). Loop diuretics may be required in these patients.

Adverse effects:

Thiazide diuretics can induce hypokalaemia, hyperuricemia and, to a lesser extent, hyperglycaemia in some patients. Thiazides increase serum uric acid by decreasing the amount of acid excreted through competition in the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

b- Loop diuretics (LD)

The loop diuretics (such as furosemide) act by blocking sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics. LD cause decreased renal vascular resistance and increased renal blood flow.

In comparison to thiazides diuretics:

Like thiazides, LD can cause hypokalaemia. However, **unlike thiazides**, LD increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease it. These agents are rarely used alone to treat HT, but they are commonly used to manage symptoms of heart failure and oedema.

In addition, LD can cause hyperuricemia as Loop diuretics compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, may cause or exacerbate gouty attacks.

- ✓ Ototoxicity : Reversible or permanent hearing loss may occur with loop diuretics, particularly when infused intravenously at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics)

c- Potassium-sparing diuretics (PSD)

PSD (such as amiloride and spironolactone (aldosterone receptor antagonists) reduce potassium loss in the urine. Aldosterone antagonists (spironolactone) have the additional benefit of diminishing the cardiac remodelling that occurs in heart failure. Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

2- β-ADRENOCEPTOR–BLOCKING AGENTS (β-BLOCKER (BB))

β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure. A summary of BB mechanism of action is demonstrated in figure 3. The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β_2-mediated bronchodilation. β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

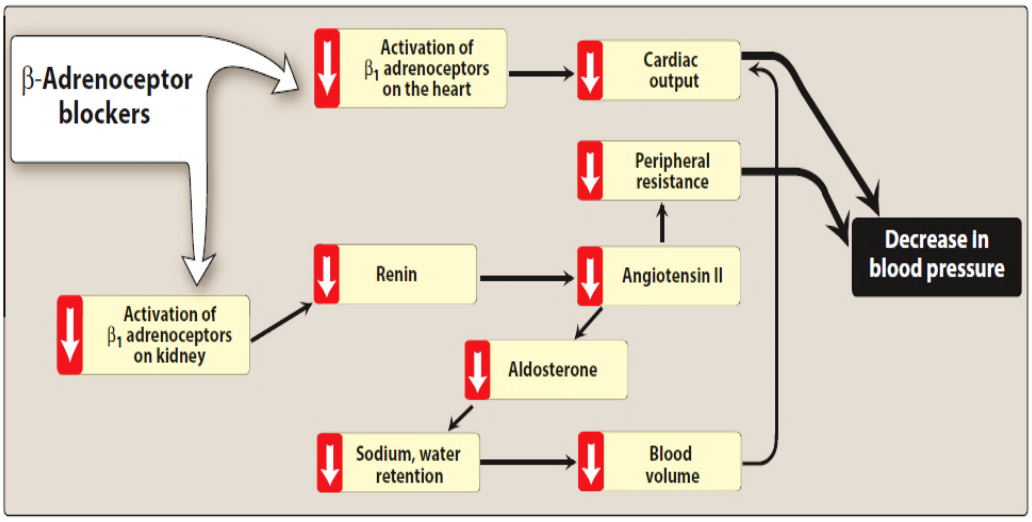


Figure 3: Actions of β-adrenoceptor–blocking agents.

Therapeutic uses

The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as previous myocardial infarction, angina pectoris, and chronic heart failure. Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma. Oral β-blockers may take several weeks to develop their full effects. Esmolol, metoprolol, and propranolol are available in intravenous formulations.

Adverse effects

Common effects: The β-blockers may cause bradycardia, hypotension, and CNS side effects such as fatigue, lethargy, and insomnia. The β-blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.

Alterations in serum lipid patterns: Non-cardioselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

Drug withdrawal: Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with HT and ischemic heart disease.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.

agonists and antagonists that are directed against specific receptor subtypes. M_1 receptor agonists are being investigated for the treatment of Alzheimer's disease and M_3 receptor antagonists for the treatment of chronic obstructive pulmonary disease. [Note: At present, no clinically important agents interact solely with the M_4 and M_5 receptors.]

B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (Figure 4.4B). 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 N_M, and the others, N_N. 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.*

IV. 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* (Figure 4.5). All of the direct-acting cholinergic drugs have a longer duration of action than ACh. The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

A. Acetylcholine

Acetylcholine [ah-see-teel-KOE-leen] 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

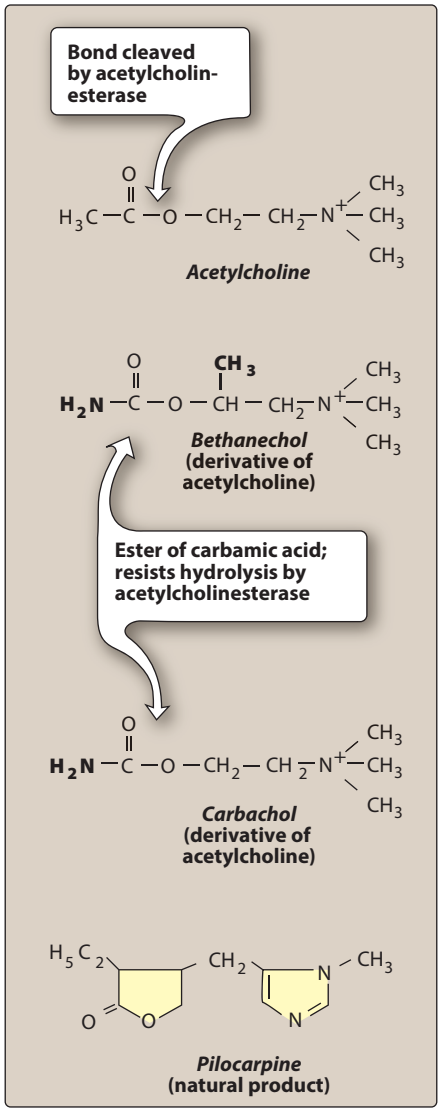


Figure 4.5
Comparison of the structures of some cholinergic agonists.

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 M_3 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 and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions. 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.

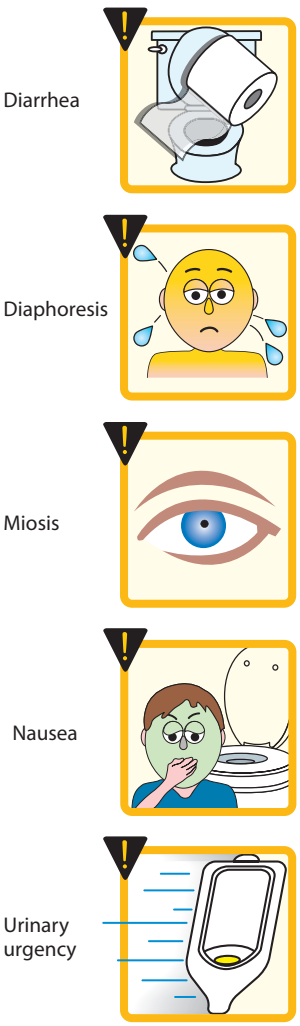


Figure 4.6
Some adverse effects observed with cholinergic agonists.

B. Bethanechol

Bethanechol [be-THAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh (Figure 4.5). 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. *Bethanechol* may also be used to treat neurogenic atony as well as megacolon.

3. **Adverse effects:** *Bethanechol* causes the effects of generalized cholinergic stimulation (Figure 4.6). 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.

C. Carbachol (carbamylcholine)

Carbachol [KAR-ba-kole] has both muscarinic and nicotinic actions. Like *bethanechol*, *carbachol* is an ester of carbamic acid (Figure 4.5) 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.

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* [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by AChE (Figure 4.5). 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 and contraction of the ciliary muscle. When the eye undergoes this miosis, it experiences a spasm of accommodation. The vision becomes fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye.] *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. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren 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.

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 as a result 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 β-adrenergic blockers such as *timolol*, are effective in treating glaucoma but are not used for

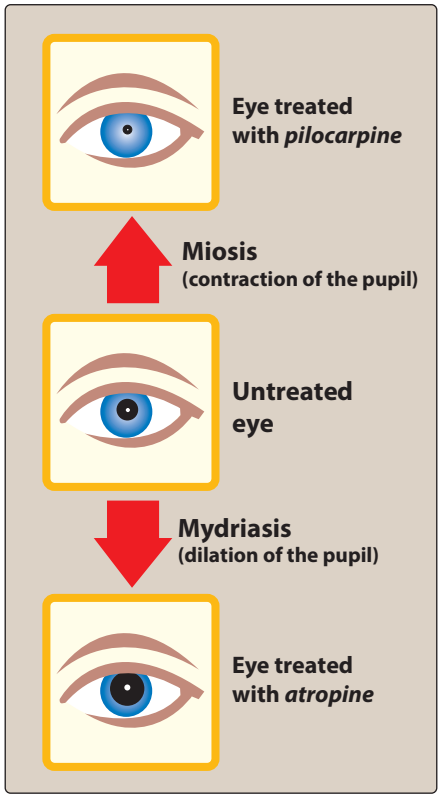


Figure 4.7
Actions of *pilocarpine* and *atropine* on the iris and ciliary muscle of the eye.

emergency lowering of intraocular pressure.] The miotic action of *pilocarpine* is also useful in reversing mydriasis due to *atropine.*

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*. Parenteral *atropine*, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of *pilocarpine.*

V. INDIRECT-ACTING 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 (Figure 4.8). 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 [ed-row-FOE-nee-um] 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. 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 after surgery. Due to the availability of other agents, *edrophonium* use has become limited.

B. Physostigmine

Physostigmine [fi-zoe-STIG-meen] 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.

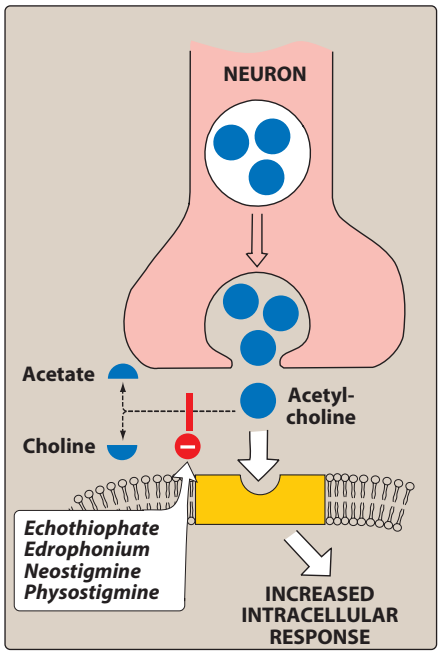


Figure 4.8
Mechanisms of action of indirect cholinergic agonists.

1. **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.

2. **Therapeutic uses:** The drug increases intestinal and bladder motility, which serves as its therapeutic action in atony of either organ (Figure 4.9). *Physostigmine* is also used in the treatment of overdoses of drugs with anticholinergic actions, such as *atropine.*

3. **Adverse effects:** 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.

C. Neostigmine

Neostigmine [nee-oh-STIG-meen] 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 and ambenonium

Pyridostigmine [peer-id-oh-STIG-meen] and *ambenonium* [am-be-NOE-nee-um] are other cholinesterase inhibitors that are used in the chronic management of myasthenia gravis. Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively) but longer than that of *neostigmine.* Adverse effects of these agents are similar to those of *neostigmine.*

E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer's disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of

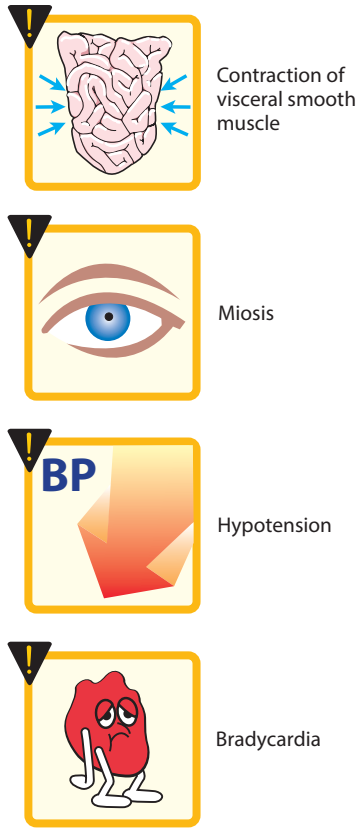


Figure 4.9
Some actions of *physostigmine.*

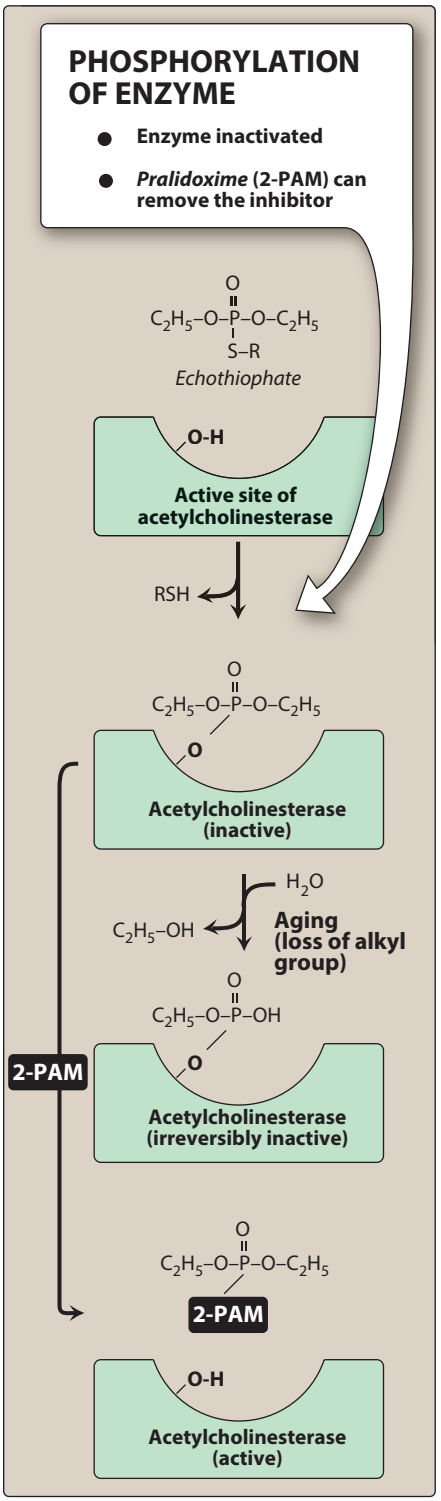


Figure 4.10
Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime*. R = $(CH_3)_3N^+–CH_2–CH_2–$; RSH = $(CH_3)_3N^+–CH_2–CH_2–S–H$.

anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* [TAK-reen] was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil* [doe-NEP-e-zil], *rivastigmine* [ri-va-STIG-meen], and *galantamine* [ga-LAN-ta-meen] to delay the progression of Alzheimer's disease, none can stop its progression. GI distress is their primary adverse effect (see Chapter 8).

VI. 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* [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 4.10). 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 causing cataracts. Figure 4.11 summarizes the actions of some of the cholinergic agonists.

VII. TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides in the United States, 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.

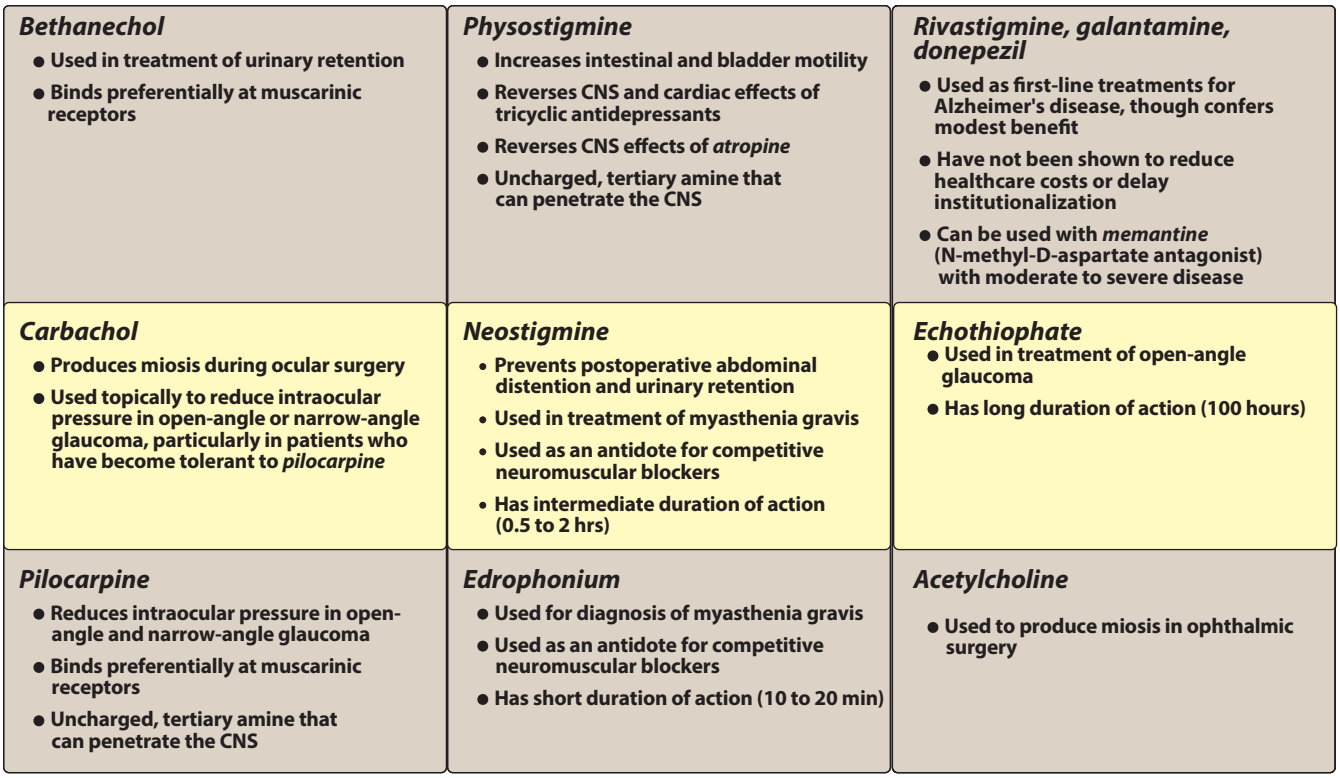


Figure 4.11
Summary of actions of some cholinergic agonists. CNS = central nervous system.

A. Reactivation of acetylcholinesterase

Pralidoxime [pral-i-DOX-eem] (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 (Figures 4.6 and 4.9). In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*).

B. 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.

Antianginal Drugs

Atherosclerotic disease of the coronary arteries (coronary artery disease (CAD) or ischemic heart disease (IHD)), is the most common cause of mortality worldwide. Atherosclerotic lesions in coronary arteries can obstruct blood flow (Figure1), leading to an *imbalance in myocardial oxygen supply and demand* that presents as stable angina or an acute coronary syndrome such as myocardial infarction (MI) or unstable angina. Spasms of vascular smooth muscles may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain.

Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms.

All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation) and management of modifiable risk factors (such as hypertension and diabetes) to reduce cardiovascular morbidity and mortality.

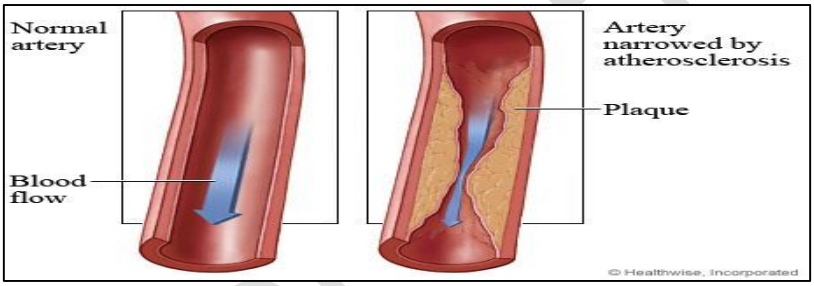


Figure 1: Blood flow in a coronary artery partially blocked with atherosclerotic plaques.

Types of Angina

Angina pectoris has three patterns: 1) stable angina; 2) unstable angina; and 3) rest angina. They are caused by varying combinations of increased myocardial oxygen demand and decreased myocardial perfusion.

A- Stable angina, effort-induced angina, classic or typical angina

Typical angina pectoris is the most common form of angina that is characterised by a short-lasting burning, heavy, or squeezing feeling in the chest.

Some ischemic episodes may present ''atypically''—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina).

Atypical presentations are more common in women, diabetic patients, and the elderly.

Classic angina is caused by

1- The reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis.

2- Increased myocardial oxygen demand, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload, may induce ischemia.

Typical angina pectoris is promptly relieved by rest or nitroglycerin (NG). **When the pattern of chest pain and the amount of effort needed to trigger the chest pain does not vary over time, the angina is named "stable angina."**

B. Unstable angina

Unstable angina is chest pain that occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort. Any episode of rest angina longer than 20 minutes, any new-onset angina or even sudden development of shortness of breath is suggestive of unstable angina. The symptoms are not relieved by rest or NG.

C. Prinzmetal, variant, vasospastic, or rest angina

is an uncommon pattern of episodic angina that occurs at rest and is due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as NG and calcium channel blockers.

Acute coronary syndrome

Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue.

MI (necrosis) is typified by increases in the serum levels of biomarkers such as troponins and creatine kinase. The acute coronary syndrome may present as ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction (Figure 2), or as unstable angina. [Note: In unstable angina, increases in biomarkers of myocardial necrosis are not present.]

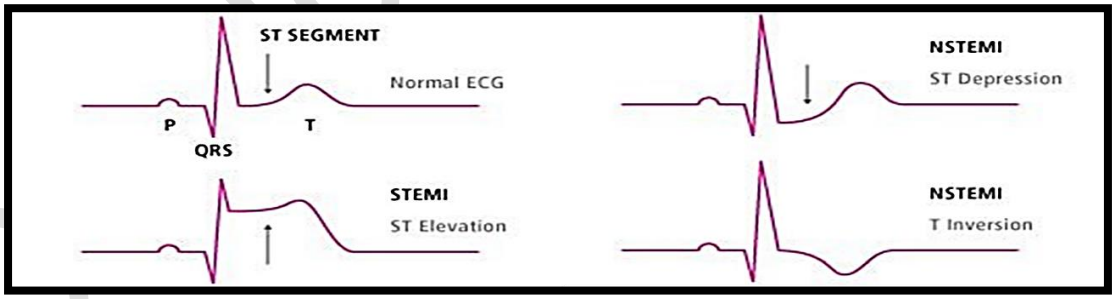


Figure 2: The differences between ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction.

Treatment Strategies

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina: β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug (ranolazine).

These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.

A treatment algorithm for patients with stable angina is demonstrated in figure 3.

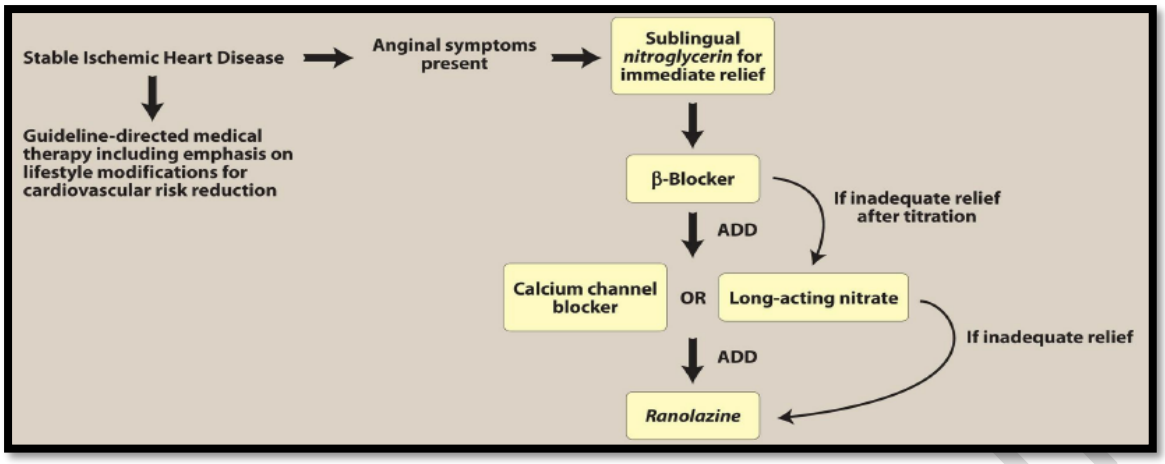


Figure 4: Treatment algorithm for improving symptoms in patients with stable angina.

Antianginal drugs mainly consist of:

1- β-Adrenergic Blockers (BBs)

- **Action:** The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and severity of angina attacks.
- **Uses:**
  - BBs can be used to increase exercise duration and tolerance in patients with effort-induced angina.
  - βBs are recommended as <u>initial antianginal therapy</u> in all patients unless contraindicated such as patients with asthma or diabetes mellites. The exception to this rule is vasospastic angina, in which βBs are ineffective and may actually worsen symptoms. βBs reduce the risk of death and MI in patients who have had a prior MI and also improve mortality in patients with heart failure with reduced ejection fraction.
- Agents with intrinsic sympathomimetic activity (ISA) such as pindolol should be avoided in patients with angina and those with a history of MI.
- Propranolol is the prototype for this class of compounds, but it is not cardioselective. Thus, other βBs, such as metoprolol and atenolol, are preferred. [Note: All βBs are nonselective at high doses and can inhibit β2 receptors.]
- **Contraindications:**
  - βBs should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely.
  - Nonselective BBs should be avoided in patients with asthma.

- It is important not to discontinue βBs therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.

2- Calcium Channel Blockers (CCBs)

❖ **Action:**

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia in response to hypoxia leading to increment in muscle tone that can worsen the case and lead to more complications. The CCBs protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- So, all CCBs are arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance. These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle.

❖ **Uses:**

- In the treatment of effort-induced angina, CCBs reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload.
- On the other hand, their efficacy in vasospastic angina is due to relaxation of the coronary arteries. [Note: Verapamil mainly affects the myocardium, whereas amlodipine exerts a greater effect on smooth muscle in the peripheral vasculature. Diltiazem is intermediate in its actions.]
- All CCBs lower blood pressure.

❖ **Dihydropyridine calcium channel blockers**

- Amlodipine, an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.
- Nifedipine is another agent in this class; it is usually administered as an extended-release oral formulation.

❖ **Nondihydropyridine calcium channel blockers**

- Verapamil slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator.
- Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- Diltiazem also slows AV conduction, decreases the rate of firing of the sinus node pacemaker and is also a coronary artery vasodilator.
- Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.
- Nondihydropyridine CCBs can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

3- Organic Nitrates

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms of angina.

Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which in turn activates guanylate cyclase and increases synthesis of cyclic guanosine monophosphate (cGMP). Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 4).

Nitrates such as NG cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

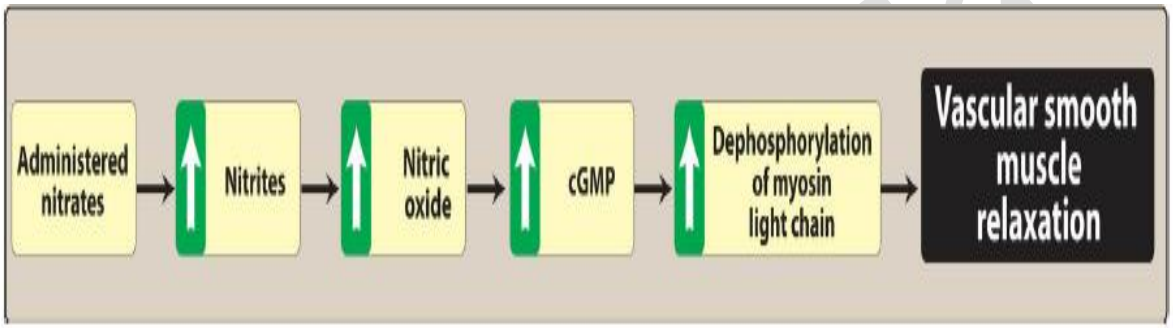


Figure 4: Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3',5'-monophosphate.

Pharmacokinetics

- Nitrates differ in their onset of action and rate of elimination. The onset of action varies from 1 minute for NG to 30 minutes for isosorbide mononitrate.
- Sublingual NG, available in tablet or spray formulation, is the drug of choice for prompt relief of an angina attack precipitated by exercise or emotional stress.
- All patients should have NG on hand to treat acute angina attacks.
- Significant first-pass metabolism of NG occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch), thereby avoiding the hepatic first-pass effect.
- Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

Adverse effects

- Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- Phosphodiesterase type 5 inhibitors such as sildenafil potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitised to vasodilation.
- Tolerance can be overcome by providing a daily “nitrate-free interval” to restore sensitivity to the drug. The nitrate free interval of 10 to 12 hours is usually taken at night when myocardial oxygen demand is decreased. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate free interval in patients with variant angina should occur in the late afternoon.
- NG patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval.

4- Sodium Channel Blocker

- Ranolazine improving the oxygen supply by reducing the intracellular sodium and calcium overload, thereby improving diastolic function.
- It has antianginal as well as antiarrhythmic properties. It is most often used in patients who have failed other antianginal therapies.
- It can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
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Drugs affecting the Cardiovascular system (Antihypertensives--part-2)

❖ ACE INHIBITORS (Angiotensin-converting enzyme (ACE) inhibitors)

The ACE inhibitors, such as enalapril and lisinopril, are recommended as **first-line treatment** of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

Actions

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.

These drugs block the enzyme angiotensin converting enzyme (ACE) which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (figure 1). ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. ACE inhibitors decrease angiotensin II and increase bradykinin levels.

So, vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin). In Addition, ACE inhibitors also decrease the secretion of aldosterone (by reducing circulating angiotensin II levels), resulting in decreased sodium and water retention. Accordingly, ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.

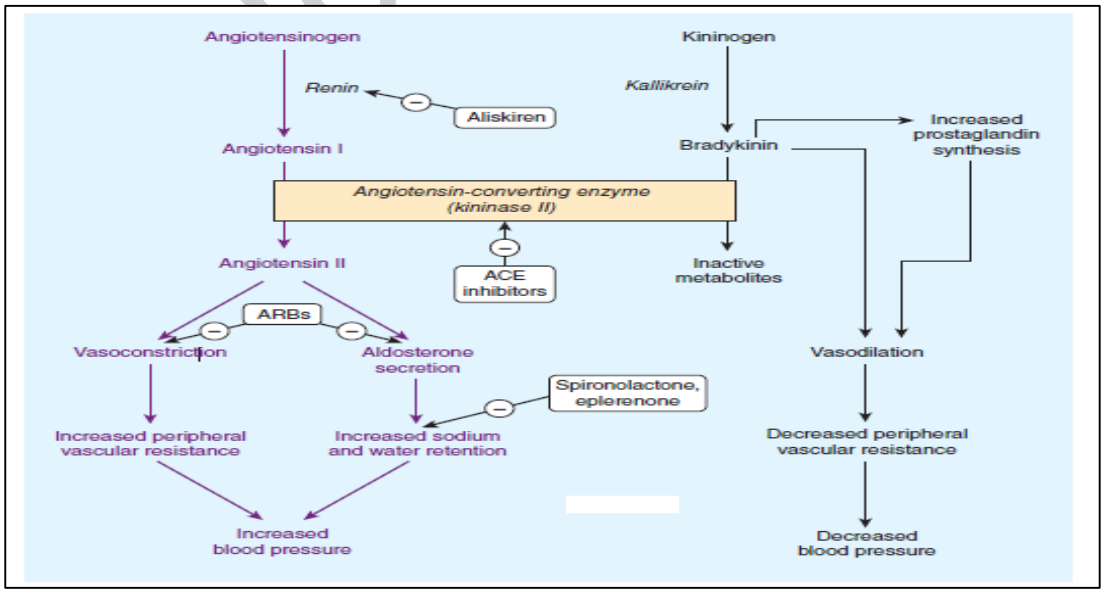


Figure 1: Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

Therapeutic uses

1- ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy.

2- ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction.

3- Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodelling after a myocardial infarction.

4- ACE inhibitors are first-line drugs for treating heart failure and hypertensive patients with chronic kidney disease. All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.

Pharmacokinetics

- All of the ACE inhibitors are orally bioavailable as a drug or prodrug. All but captopril and lisinopril undergo hepatic conversion to active metabolites, so these agents may be preferred in patients with severe hepatic impairment.
- Fosinopril is the only ACE inhibitor that is not eliminated primarily by the kidneys and does not require dose adjustment in patients with renal impairment.
- Enalaprilat is the only drug in this class available intravenously.

Adverse effects

- **Common side effects** include dry cough, rash, fever, altered taste, hypotension (in hypovolemic states), and hyperkalaemia. The dry cough, which occurs in up to 10% of patients, is thought to be due to increased levels of bradykinin and substance P in the pulmonary tree and resolves within a few days of discontinuation.
- Angioedema is a rare but potentially life-threatening reaction that may also be due to increased levels of bradykinin.
- Potassium levels must be monitored while on ACE inhibitors, and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalaemia.
- Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease.
- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

- ✓ The ARBs, such as losartan and irbesartan, are alternatives to the ACE inhibitors. These drugs block the AT_1 receptors, decreasing the activation of AT_1 receptors by angiotensin II.

- ✓ Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention (figure 1).
- ✓ ARBs do not increase bradykinin levels. They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.
- ✓ Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.
- ✓ ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects.
- ✓ These agents are also teratogenic and should not be used by pregnant women.

❖ RENIN INHIBITOR

- A selective renin inhibitor, aliskiren, is available for the treatment of hypertension. Aliskiren directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs (figure 1).
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides. Aliskiren should not be routinely combined with an ACE inhibitor or ARB.
- Aliskiren can cause diarrhoea, especially at higher doses, and can also cause cough and angioedema but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is contraindicated during pregnancy.

❖ CALCIUM CHANNEL BLOCKERS (CCB)

Calcium channel blockers are a recommended treatment option in hypertensive patients with diabetes or angina. High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications

1. Diphenylalkylamines: Verapamil is the only member of this class and it is the least selective of any calcium channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2. Benzothiazepines: Diltiazem is the only member of this class that is currently approved in the United States. Like verapamil, diltiazem affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of verapamil. Diltiazem has a favourable side effect profile.

3. Dihydropyridines: This class of calcium channel blockers includes many drugs such as the nifedipine (the prototype), amlodipine and felodipine, which differ in pharmacokinetics, approved uses, and drug interactions.

All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly beneficial in treating hypertension. The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium channel blockers.

Actions

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage sensitive calcium channels. This triggers the intracellular release of calcium, which further increases the cytosolic level of calcium. Calcium channel antagonists block the inward movement of calcium by binding to L type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

Therapeutic uses

1- In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy. They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike β-blockers, they do not have the potential to adversely affect these conditions.
2- All CCBs are useful in the treatment of angina.
3- In addition, diltiazem and verapamil are used in the treatment of atrial fibrillation.

Pharmacokinetics

Most of these agents have short half-lives (3 to 8 hours) following an oral dose. Sustained-release preparations are available and permit once-daily dosing. Amlodipine has a very long half-life and does not require a sustained-release formulation.

Adverse effects

1- First-degree atrioventricular block and constipation are common dose dependent side effects of verapamil. Verapamil and diltiazem should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.
2- Dizziness, headache and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines. Peripheral oedema is another commonly reported side effect of this class. **Nifedipine and other dihydropyridines may cause gingival hyperplasia.**

❖ α-ADRENOCEPTOR–BLOCKING AGENTS

Prazosin, doxazosin, and terazosin produce a competitive block of α1-adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension.

❖ α-/β-ADRENOCEPTOR–BLOCKING AGENTS

Labetalol and carvedilol block α_1, β_1, and β_2 receptors. Carvedilol, although an effective antihypertensive, is mainly used in the treatment of heart failure. Carvedilol, as well as metoprolol succinate, and bisoprolol have been shown to reduce morbidity and mortality associated with heart failure. Labetalol is used in the management of gestational hypertension and hypertensive emergencies.

❖ CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

- Clonidine acts centrally as an α_2 agonist to produce inhibition of sympathetic vasomotor centres, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.
- It does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
- Adverse effects include sedation, dry mouth, and constipation. Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should, therefore, be withdrawn slowly if discontinuation is required.

B. Methyldopa

Methyldopa is an α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. The most common side effects of methyldopa are sedation and drowsiness. Its use is limited due to adverse effects and the need for multiple daily doses. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

❖ VASODILATORS

1- The direct-acting smooth muscle relaxants, such as hydralazine and minoxidil, are not used as primary drugs to treat hypertension.

2- These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure.

3- Hydralazine is an accepted medication for controlling blood pressure in pregnancy induced hypertension. Adverse effects of hydralazine include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina.

4- Minoxidil treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a rare but life-threatening situation characterised by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, myocardial infarction).
- A severe elevation in blood pressure without evidence of target organ damage is considered a hypertensive urgency.
- Hypertensive emergencies require timely blood pressure reduction with treatment administered intravenously to prevent or limit target organ damage.
- A variety of medications are used such as calcium channel blockers, adrenergic receptor antagonists (labetalol), the vasodilator and hydralazine.
- Treatment is directed by the type of target organ damage present and/or comorbidities present.

RESISTANT HYPERTENSION

Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension are:

1- Poor compliance, excessive ethanol intake, and concomitant conditions (diabetes, obesity).
2- Moreover, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (nonsteroidal anti-inflammatory drugs, or antidepressant medications), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

COMBINATION THERAPY

- Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects.
- Initiating therapy with two antihypertensive drugs should be considered in patients with blood pressures that are more than 20/10 mm Hg above the goal.
- A variety of combination formulations of the various pharmacologic classes are available to increase ease of patient adherence to treatment regimens that require multiple medications to achieve the blood pressure goal.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.

Pharmacology

Lec. 3+4 College of dentistry

Dr Maha Mohsin Khalaf University of Baghdad

Autonomic 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 (figure 1)

The autonomic nervous system (ANS) is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life.

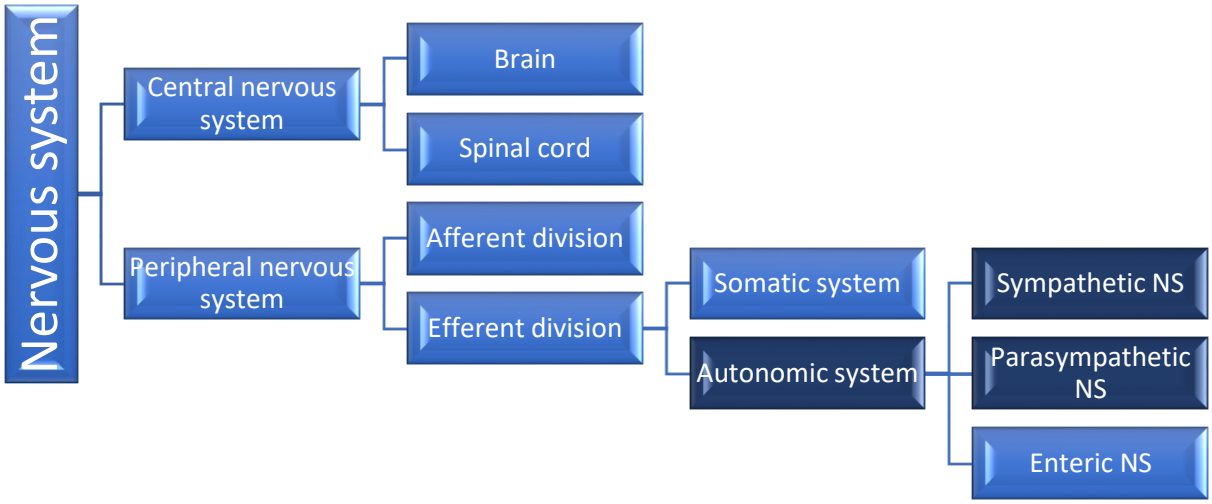


Figure 1: autonomic nervous system part of nervous system

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. In this pre and post ganglionic complex the ganglia function is embodied in acting as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron (figure 2)

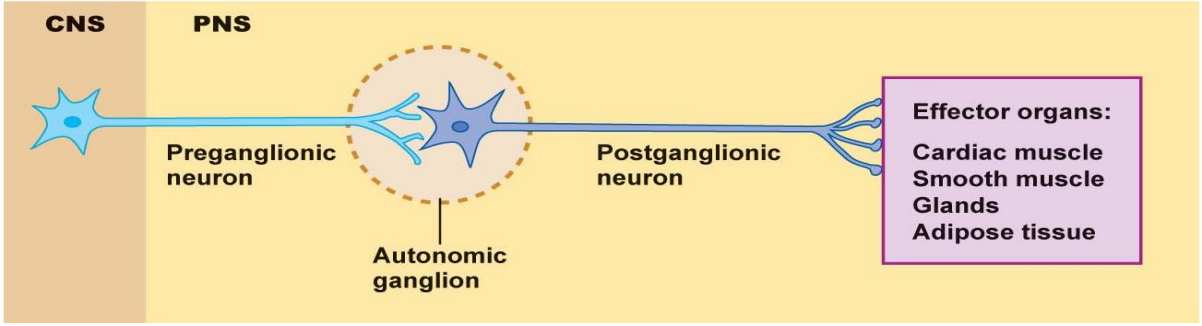


Figure 2: preganglionic and post ganglionic neurons

The function of the ANS can be explained by exploring the function of each part as the following:

A) Functions of the sympathetic nervous system

1- Effects of stimulation of the sympathetic division: The effect of sympathetic output is to:

1. Increasing heart rate and contractility, and thus, increasing blood pressure.
2. Constriction of the blood vessels of skin, mucous membranes, and splanchnic area, and dilation of skeletal muscles vessels.
3. Dilation of the pupils (mydriasis).
4. Bronchodilation.
5. Inhibit salivation.
6. Decrease GI motility.
7. Stimulation of ejaculation.
8. Inhibit bladder contraction.
9. Stimulate glucose production and release.

2- Fight-and-flight response: The changes experienced by the body during emergencies are referred to as the "fight and 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.

Accordingly, the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycaemia, cold, and exercise.

B) **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 fibres innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

So, the effect of parasympathetic output can be summarised in:

1- Pupil contraction (miosis).
2- Bronchoconstriction.
3- Stimulation of erection.

4- Stimulation tears and saliva secretion.
5- Decreasing heart rate and contractility.
6- Increasing the muscle motility and tone of the gastrointestinal system.

C) **Functions of the enteric nervous system (ENS)**

The enteric nervous system is a collection of neurons in the gastrointestinal tract that constitutes the "brain of the gut" and can function independently of the central nervous system. This system controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract.

D) **Functions of the somatic nervous system**

The somatic system is the part of the peripheral nervous system that is responsible for carrying motor and sensory information both to and from the central nervous system *without the mediation of ganglia*. This system is made up of nerves that connect to the skin, sensory organs, and all skeletal muscles. The system is responsible for nearly all voluntary muscle movements as well as for processing sensory information that arrives via external stimuli including hearing, touch, and sight.

The ANS requires 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 centres in the CNS, such as the hypothalamus and spinal cord. These centres respond to the stimuli by sending out efferent reflex impulses via the ANS. **This process of initiating an afferent impulse that travel to the CNS and replying by efferent impulse to get a response is called *reflex arc*** (figure 3).

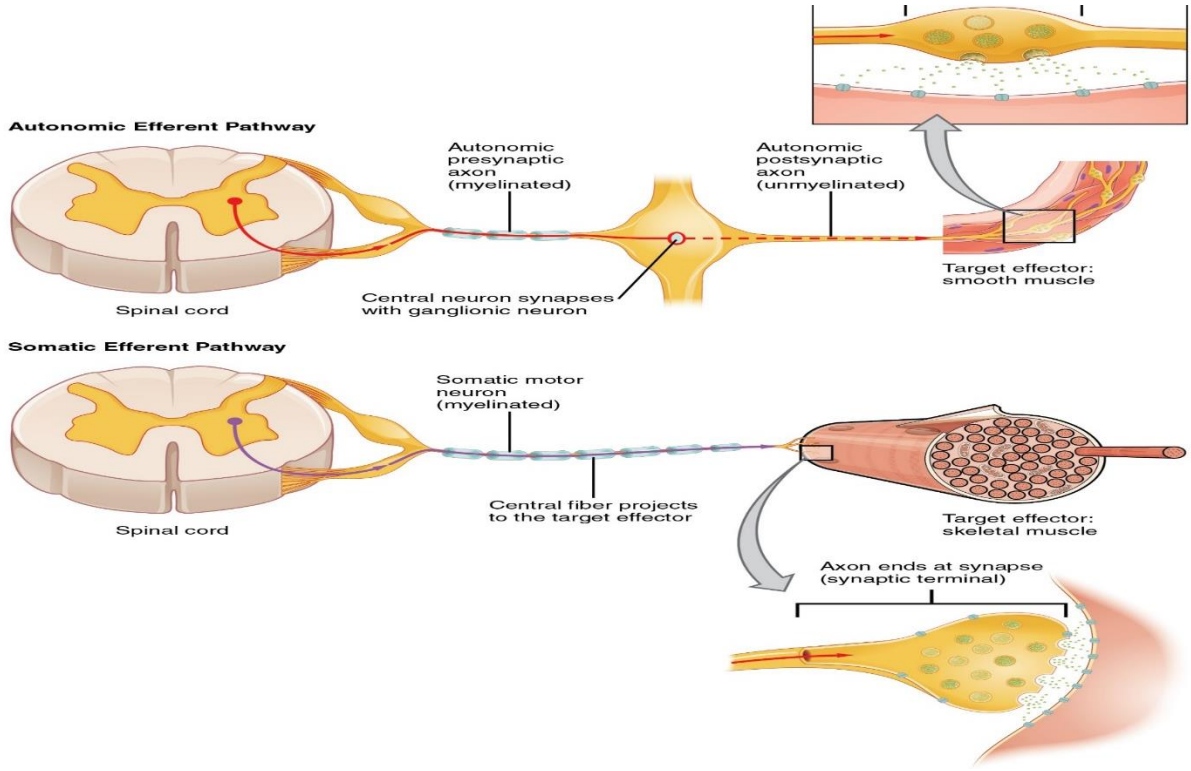


Figure 3: Somatic and autonomic reflex arc

Usually, most of the afferent impulses are involuntary translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centres in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and tachycardia.

According to the above explanation, the reflex arcs of the ANS comprise a sensory (or afferent) arm and a motor (or efferent or effector) arm.

Neurotransmitters

Neurotransmission in the ANS is an example of the more general process of chemical signalling between cells using neurotransmitters. Neurotransmitters are specific chemical signals that are released from nerve terminals to establish the communication between nerve cells, and between nerve cells and effector organs.

In spite of recognising more than 50 signals molecules (neurotransmitters) in the nervous system, just norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are the most commonly involved neurotransmitters in the actions of therapeutically useful drugs. Each type of neurotransmitters can bind with a specific receptor in order to give the biological desirable response.

The primary chemical signals in the ANS are the acetylcholine and norepinephrine as they are involved in conducting wide variety functions in the CNS.

The autonomic nerve fibres can be classified to cholinergic and adrenergic neurons based on the type of the released neurotransmitters whether they are acetylcholine or epinephrine and norepinephrine.

Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs also involve the release of acetylcholine (figure 4). In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibres and voluntary muscles) is also cholinergic.

In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs except few sympathetic fibres, such as those involved in sweating, are cholinergic.

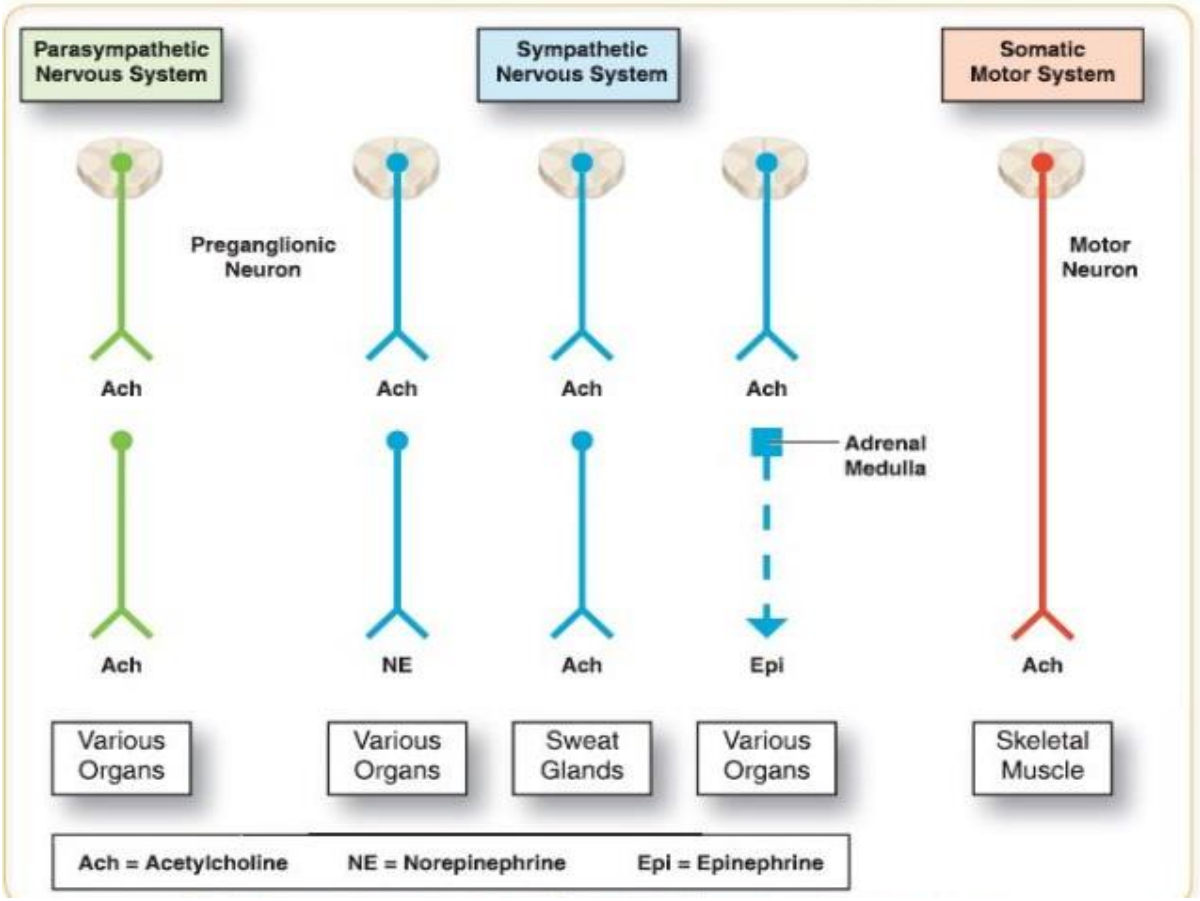


Figure 4: Neurotransmitters

Cholinergic agonists

The cholinergic drugs act on receptors that are activated by acetylcholine (ACh). These receptors include nicotinic and muscarinic receptors and can be mainly recognised in sympathetic and parasympathetic nervous system and somatic nervous system as well (Figure 5).

The two classes of receptor for Ach are defined on the basis of their preferential activation by the alkaloids *nicotine* and *muscarine.*

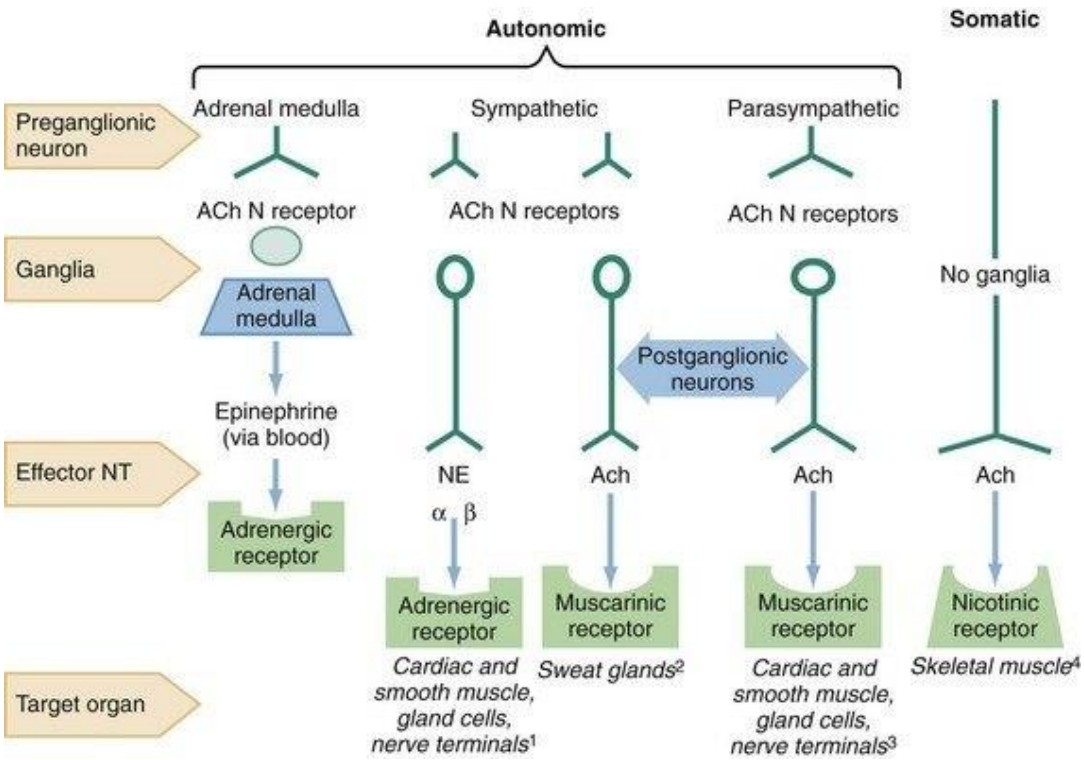


Figure 5: Ach receptors muscarinic and nicotinic receptors, the nicotinic receptors located on autonomic ganglia (Nn subtype) and on neuromuscular junction on somatic nervous system (Nm subtype)

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 (figure 6)

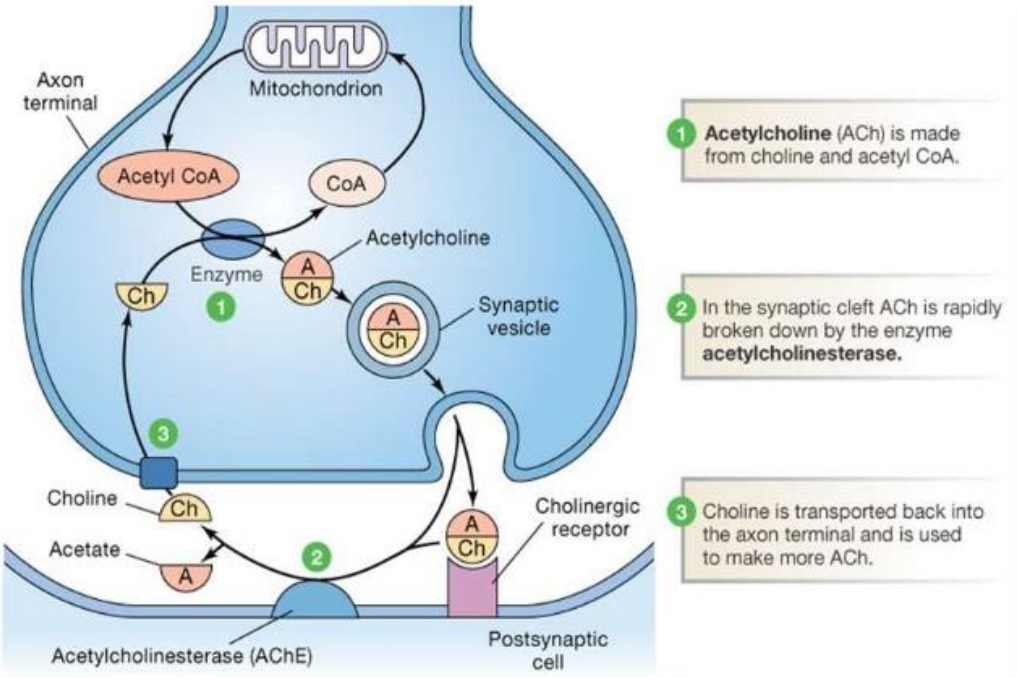


Figure 6: Ach synthesis

1.Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system. 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.

3.Release of acetylcholine: When an action potential propagated 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.

4.Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds its 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.

5. Degradation of acetylcholine: The signal at the postjunctional effector site is rapidly terminated, because AChE (acetylcholine esterase) cleaves ACh to choline and acetate in the synaptic cleft.

6. Recycling of choline: Choline may be recaptured by a sodium-coupled uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Cholinoceptors can be classified into two types: muscarinic and nicotinic receptors. They are different mainly in their affinities for agents that mimic the action of ACh (cholinomimetic agents).

1- **Muscarinic receptors:** It is one of the G protein–coupled receptors that have high affinity to bind with muscarine (an alkaloid that is present in certain poisonous mushrooms) and ACh but low affinity to bind with nicotine. Five sub-classes are recognised for this receptor family; however, only M1, M2, and M3 receptors have been functionally characterised.

   a- **Locations of muscarinic receptors:** These receptors are found:
   - On ganglia of the peripheral nervous system.
   - On the autonomic effector organs (such as the heart, smooth muscle, brain, and exocrine glands).
   - In addition, 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.

   b- **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.

2- Nicotinic receptors

These receptors, in addition to binding ACh, also recognise nicotine but show only a weak affinity for muscarine. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. The nicotinic receptor functions as a ligand-gated ion channel.

Location: 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 N_M, and the others, N_N. 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

Definition: Materials that mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic).

Types:

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

2) Naturally occurring alkaloids, such as *nicotine* and *pilocarpine.* The main advantage of this group of drugs that have a longer duration of action than ACh.

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

Acetylcholine

Acetylcholine is a quaternary ammonium compound; hence it cannot penetrate membranes. In spite of considering the ACh as a neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its pluralism of actions 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 imitate 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.

2- **Decrease in blood pressure:** As a result of ACh injection, vasodilation and lowering of blood pressure can be observed. This is due to an indirect mechanism of action because the ACh activates M3 receptors that found on endothelial cells lining the smooth muscles of blood vessels. This leads to produce a nitric oxide that act as a vasodilator from arginine. 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**

ACh administration can stimulate:

a- Salivary secretion stimulates intestinal secretions and motility.

b- Bronchiolar secretions.

c- Urination.

Moreover, ACh causes miosis (marked constriction of the pupil). Accordingly, ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

Therapeutic uses of direct-acting cholinergic agonists:

- ✓ bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.
- ✓ Carbachol eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.
- ✓ Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure in glaucoma. It is also beneficial in promoting salivation in patients with xerostomia (dry mouth) resulting from irradiation therapy of the head and neck cancer or due to Sjogren's syndrome (an autoimmune disease in which the moisture-producing glands of the body are affected causing mainly symptoms of dry eyes and dry mouth).

Adverse effects of Ach and other cholinergic agonists: causes the effects of generalized cholinergic stimulation.

- Bronchospasm and increase secretions.
- GI: nausea, vomiting, and diarrhea.
- Miosis.
- Urinary urgency.
- Sweating (diaphoresis) and salivation.
- *Pilocarpine* can enter the brain (because it's a tertiary amine (unionized)) and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects.

To counteract the poisoning effect of the pilocarpine and Bethanechol, Parenteral *atropine*, at doses that can cross the blood–brain barrier, is administered to counteract the toxicity of *the cholinergic material.*

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTERASE AGENTS (REVERSIBLE))

ACh is uaually deactivated by the AChE (Acetylcholine esterase), which is an enzyme that specifically cleaves ACh to acetate and choline. It can be found at both pre- and postsynaptically in the nerve terminal where it is membrane bound.
Accordingly, inhibition of AchE can indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. This process can be carried out by using the anticholinesterase agents or cholinesterase inhibitors. 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.

Therapeutic uses of acetylcholinesterase inhibitors (reversible)

Edrophonium, pyridostigmine, and ambenonium: They are used in the diagnosis and management of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter.

Physostigmine

- It increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ.
- used to treat glaucoma, but *pilocarpine* is more effective.
- as an antidote for drugs with anticholinergic actions.

Neostigmine

- used to stimulate the bladder and GI tract.
- as an antidote for *tubocurarine* and other competitive neuromuscularblocking agents.
- also used to treat myasthenia gravis.

Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* was the first to become available, but it 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.

Adverse effects of acetylcholinesterase inhibitors (reversible):

- Adverse effects include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

- Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle.
- *Physostigmine* can enter and stimulate the cholinergic sites in the CNS. The effects on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur.

INDIRECT-ACTING CHOLINERGIC AGONISTS (ANTICHOLINESTRASE 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.

Table: Summary of echothiophate actions, therapeutic uses and its adverse effect.

Anticholinesterase agent (Irreversible)	**Actions**	**Therapeutic uses**	**Adverse effect**
Echothiophate	*Covalently binds to the AChE.	*A topical solution of the drug is for the treatment of open-angle glaucoma.	*Represented by the generalised cholinergic stimulation. *Paralysis of motor function (causing breathing difficulties). *Convulsions.

Cholinergic Antagonists

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.

There are three types of cholinergic antagonist drugs, which are:

1- Antimuscarinic agents (anticholinergic drugs) block muscarinic receptors, causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs).

2- Ganglionic blockers (specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia)

3- The neuromuscular-blocking agents (mostly nicotinic antagonists), which block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle

1- Atropine (antimuscarinic agents): It is an 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.

Effects:

- CNS: confusion, delirium.
- Decrease GI motility and acid secretions without interfering with hydrochloric secretion.
- Increase heart rate at high doses, i.e. higher than (0.5 mg). At low doses slight decrease in heart rate.
- Decrease body secretions like saliva (xerostomia), bronchial secretions, and sweat (elevate body temperature).
- Mydriasis (cycloplegic to permits the measurement of refractive errors without interference by the accommodative capacity of the eye).

Therapeutic uses:

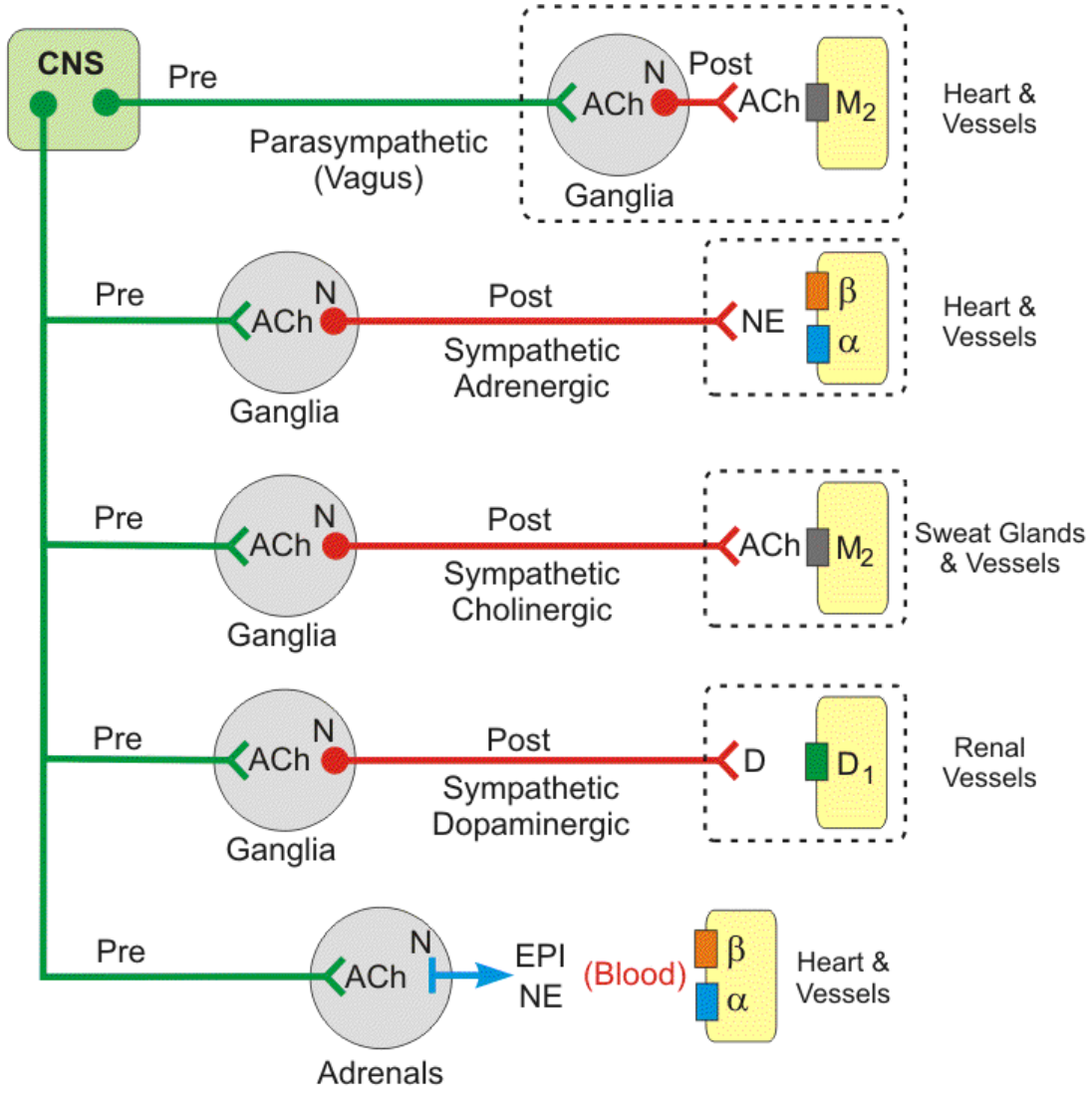
- Treatment of bradycardia.
- In ophthalmology to cause cycloplegia and mydriasis.
- Antimotility agent to treat diarrhea.
- Antisecretory agent to block the secretions in the upper and lower respiratory tracts before surgery.

Side effects: Blurred vision, decrease secretions, hyperthermia, constipation, urinary retention, delirium, and hallucinations.

- ✓ ***Scopolamine*** is another antagonist used for motion sickness.
- ✓ ***Ipratropium*** used as inhaler to decrease bronchoconstriction and bronchial secretions in COPD (chronic obstructive pulmonary disease) and asthma.

2- Nicotine (Ganglionic blockers)**:** although nicotine considers as an agonist at nicotinic receptors, but at higher does it blocks the autonomic ganglia (figure 7). Nicotine produces initial stimulation and varying degrees of subsequent block through a mechanism analogous to that of succinylcholine (see later).

Nicotine is a component of cigarette smoke, is a poison with many undesirable actions. However, it can be used in a controlled way to help in giving up smoking. It is found in more than one pharmaceutical dosage forms like sublingual tablets, lozenges and as chewing gum. Its action can be summarised in these points: Increasing the blood pressure and cardiac rate and at higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.



CNS = central nervous system; Pre = preganglionic; Post = postganglionic;
ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine;
D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor;
D_1 = dopaminergic receptor

Figure 7: position of nicotinic receptor in autonomic ganglia

3- The neuromuscular-blocking agents: These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the skeletal muscle. They possess some chemical similarities to ACh, and they act either as antagonists (nondepolarising type) or as agonists (depolarising type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anaesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression.

1- Nondepolarising (competitive) blockers: At low doses: Nondepolarising agents competitively block ACh at the nicotinic receptors. That is, they compete with ACh at the receptor without stimulating it. Thus, these drugs prevent depolarisation of the muscle cell membrane and inhibit muscular contraction. On the other hand, **on high**

doses, these drugs can lead to complete blockade and the muscle does not respond to direct electrical stimulation. All neuromuscular-blocking agents are injected intravenously or occasionally intramuscularly since they are not effective orally. In general, these agents are safe with minimal side effects; however, they can rarely cause bronchospasm.

2- **Depolarising agents:** Depolarising blocking agents work by depolarising the plasma membrane of the muscle fibre, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarise the muscle fibres. *Succinylcholine* is the only depolarising muscle relaxant in use today. *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarise the junction. This leads to a transient twitching of the muscle. Continued binding of the depolarising agent renders the receptor incapable of transmitting further impulses leading to flaccid paralysis. Therapeutically, *succinylcholine (which is administered IV)* is useful when rapid endotracheal intubation is required during the induction of anaesthesia. The main side effects of this drug are the hyperthermia, apnea and hyperkalaemia.