**Lecture N3**

**II Lecture: Drugs affecting efferent innervation. The concept of the adrenergic neurotransmitter system. Pharmacology of drugs affecting the adrenergic system.**

This lecture describes 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. Some sympathomimetics directly activate adrenergic receptors (direct acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists). This chapter describes agents that either directly or indirectly stimulate adrenoceptors.

*THE ADRENERGIC NEURON*

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

*Neurotransmission at adrenergic neurons*

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

*1. Synthesis of norepinephrine:*

Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then  
decarboxylated by the enzyme aromatic L-amino acid decarboxylase to form dopamine in the presynaptic neuron.

*2.Storage of norepinephrine in vesicles:* Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by reserpine. Next, dopamine is hydroxylated to form norepinephrine by the enzyme  
dopamin-hydroxylase.  
*3. 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 and expel their contents into the synapse. Drugs such as guanethidine block this release.  
*4.* *Binding to receptors:* Norepinephrine released from the synaptic  
vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in  
the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both 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 that modulate the release of the neurotransmitter.

*5. 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-0-methyltransferase (COMT) in the synaptic space, or 3) undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves  
a sodium-chloride (Na+/CI-)-dependent norepinephrine transporter that can be inhibited by tricyclic antidepressants (TCAs), such as imipramine; by serotonin-norepinephrine reuptake inhibitors such as duloxetine; or by cocaine. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

*6. 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.

*Adrenergic receptors (adrenoreceptors).*

In the sympathetic nervous system, several classes of adrenoceptors  
can be distinguished pharmacologically. Two main families of receptors, designated a and p, are classified based on response to the  
adrenergic agonists epinephrine, norepinephrine, and isoproterenol.Both the a and b receptor types have a number of specific receptor  
subtypes. Alterations in the primary structure of the receptors influence their affinity for various agents.

alfa-Adrenoceptors: The a-adrenoceptors show a weak response  
to the synthetic agonist *isoproterenol,* but they are responsive to  
the naturally occurring catecholamines *epinephrine* and *norepinephrine*.

Alfa- Receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as a-adrenergic, involving constriction of smooth muscle.

Activation of *a1-receptors* initiates a series of reactions through the G-protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 initiates the release of Ca2+ from the  
endoplasmic reticulum into the cytosol, and DAG turns on  
other proteins within the cell.

*alfa2- Receptors* are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is  
stimulated, a portion of the released norepinephrine "circles  
back" and reacts with alfa-receptors on the presynaptic membrane. Stimulation of alfa2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. [Note: In this  
instance, by inhibiting further output of norepinephrine from  
the adrenergic neuron, these receptors are acting as inhibitory auto-receptors.]

*alfa2-Receptors* are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and  
interact with these receptors, inhibiting acetylcholine release.  
[Note: In these instances, these receptors are behaving as  
inhibitory heteroreceptors.] This is another mechanism to  
modulate autonomic activity in a given area. In contrast to a1  
receptors, the effects of binding at *alfa2-receptors* are mediated  
by inhibition of adenylyl cyclase and by a fall in the levels of  
intracellular cAMP.

The beta-adrenoceptors can be subdivided into three major subgroups, b1, b2 and b3, based on their affinities for adrenergic agonists and antagonists. b1 receptors have approximately equal affinities for *epinephrine* and *norepinephrine,*whereas *b2-receptors* have a higher affinity for *epinephrine* than for *norepinephrine.* Thus, tissues with a predominance of *b2-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 b receptors results in activation of adenylyl cyclase and  
increased concentrations of cAMP within the cell.

*Distribution of receptors:*

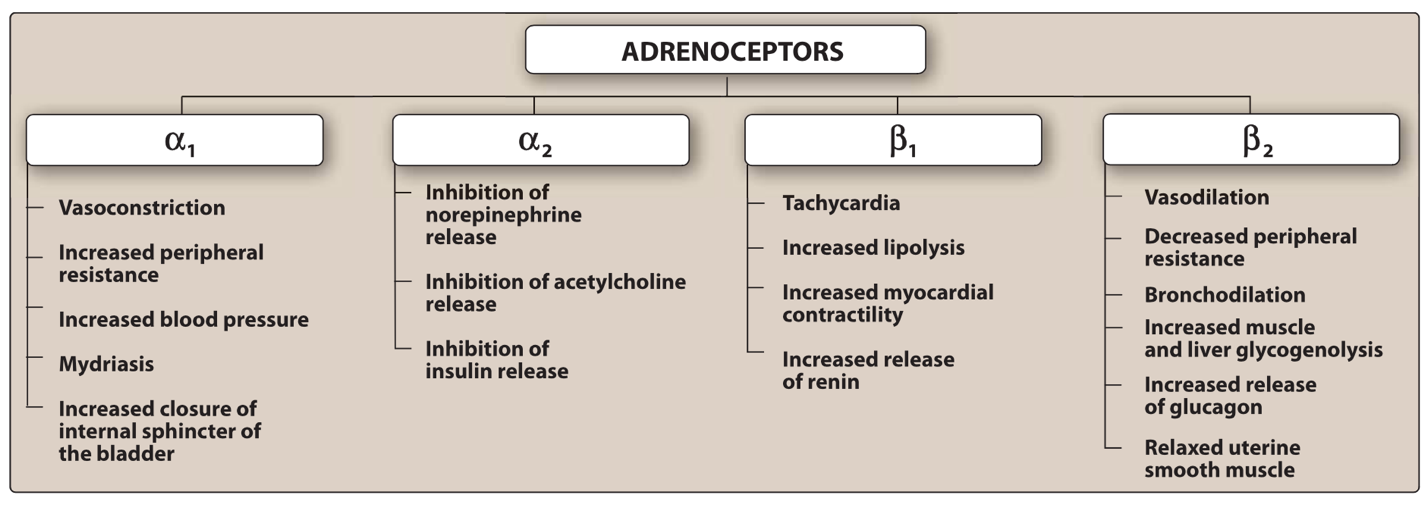
Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, tissues such as the vasculature of skeletal muscle have both *alfa1* and *beta2-receptors*, but the *b2-receptors* predominate. Other tissues  
may have one type of receptor almost exclusively. For example,  
the heart contains predominantly b1 receptors.

*Characteristic responses mediated by adrenoceptors:*

It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially  
stimulate or block one type of receptor. On the picture summarizes the  
most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of *alfa1-receptors* characteristically produces  
vasoconstriction (particularly in skin and abdominal viscera) and  
an increase in total peripheral resistance and blood pressure.  
Stimulation of *beta1-receptors* characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation  
of *b2-receptors* produces vasodilation (in skeletal muscle vascular  
beds) and smooth muscle relaxation. *B3-Receptors* are involved  
in lipolysis (along with *b1*), and also have effects on the detrusor  
muscle of the bladder.

*5. 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.



***CHARACTERISTICS OF ADRENERGIC AGONISTS***

Most adrenergic drugs are derivatives of p-phenylethylamine.  
Substitutions on the benzene ring or on the ethylamine side chains  
produce a variety of compounds with varying abilities to differentiate  
between a and p receptors and to penetrate the CNS. Two important  
structural features of these drugs are 1) the number and location of OH  
substitutions on the benzene ring and 2) the nature of the substituent on  
the amino nitrogen.

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

*1. High potency:* Catecholamines show the highest potency in  
directly activating a or preceptors.

*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.  
*B. Noncatecholamines.*

Compounds lacking the catechol hydroxyl groups have longer halflives, 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 non-catecholamines (due to lack of polar hydroxyl groups)  
permits greater access to the CNS.

*Mechanism of action of adrenergic agonists*

*1. Direct-acting agonists:* These drugs act directly on a or p 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* or cause the release of *norepinephrine* from the cytoplasmic pools or vesicles of the adrenergic neuron. The *norepinephrine* then traverses the synapse and  
binds to alfa or beta-receptors. Examples of reuptake inhibitors and  
agents that cause *norepinephrine* release include *cocaine* and  
*amphetamine,* respectively.

*3. Mixed-action agonists:* *Ephedrine* and its stereoisomer, *pseudoephedrine,* both stimulate adrenoceptors directly and enhance release of *norepinephrine* from the adrenergic neuron.

***DIRECT-ACTING ADRENERGIC AGONISTS***

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

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

*Therapeutic uses:*

*Bronchospasm:* *Epinephrine* is the primary drug used in the  
emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of anaphylactic shock, *epinephrine* is the drug of choice and can be lifesaving in this setting. Within a few minutes after subcutaneous administration, respiratory function  
greatly improves.

*Anaphylactic shock:* *Epinephrine* is the drug of choice for  
the treatment of type I hypersensitivity reactions (including  
anaphylaxis) in response to allergens.

*Cardiac arrest:* *Epinephrine* may be used to restore cardiac  
rhythm in patients with cardiac arrest.

*Local anesthesia:* Local anesthetic solutions may contain  
low concentrations (for example, 1:100,000 parts) of *epinephrine. Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. *Epinephrine* also reduces systemic absorption of the local anesthetic and promotes local hemostasis.

*Intraocular surgery:* *Epinephrine* is used in the induction  
and maintenance of mydriasis during intraocular surgery.

*Pharmacokinetics:* *Epinephrine* has a rapid onset but a brief  
duration of action (due to rapid degradation). The preferred route  
for anaphylaxis in the outpatient setting is intramuscular (anterior  
thigh) due to rapid absorption. In emergencies, *epinephrine* is  
given intravenously (IV) for the most rapid onset of action. It may  
also be given subcutaneously, by endotracheal tube, or by inhalation. It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.

*Adverse effects:* *Epinephrine* can produce adverse CNS effects  
that include anxiety, fear, tension, headache, and tremor. It can  
trigger cardiac arrhythmias, particularly if the patient is receiving *digoxin. Epinephrine* can also induce pulmonary edema due to increased afterload caused by vasoconstrictive properties of the drug. Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading  
to an enhanced response to *epinephrine,* and the dose must be  
reduced in these individuals. Inhalation anesthetics also sensitize  
the heart to the effects of *epinephrine,* which may lead to tachycardia. *Epinephrine* increases the release of endogenous stores of glucose. In diabetic patients, dosages of *insulin* may have to be increased. Nonselective beta-blockers prevent vasodilatory effects of *epinephrine* on beta2-receptors, leaving alfa receptor stimulation  
unopposed. This may lead to increased peripheral resistance and  
increased blood pressure.

*Norepinephrine* is the neurotransmitter in the adrenergic neurons, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the a-adrenergic receptor is most affected.

*Cardiovascular actions*

*Vasoconstriction:* *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (a1 effect). Both systolic and diastolic blood pressures increase. [Note: *Norepinephrine*causes greater vasoconstriction than *epinephrine,* because it  
does not induce compensatory vasodilation via beta2 receptors on  
blood vessels supplying skeletal muscles. The weak beta2 activity  
of *norepinephrine* also explains why it is not useful in the treatment of bronchospasm or anaphylaxis.]

*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.

*Therapeutic uses:* *Norepinephrine* is used to treat shock (for  
example, septic shock), because it increases vascular resistance  
and, therefore, increases blood pressure. It has no other clinically  
significant uses.

*Pharmacokinetics:* *Norepinephrine* is given IV for rapid onset of  
action. The duration of action is 1 to 2 minutes, following the end of the infusion. It is rapidly metabolized by MAO and COMT, and  
inactive metabolites are excreted in the urine.

*Adverse effects:* These are similar to *epinephrine.* In addition,  
*norepinephrine* is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein.

*Dopamine* is the immediate metabolic precursor of *norepinephrine,* occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate alfa and beta-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating a1  
receptors, whereas at lower doses, it stimulates beta1 cardiac receptors.  
In addition, D1 and D2 dopaminergic receptors, distinct from the a- and  
b-adrenergic receptors, occur in the peripheral mesenteric and renal  
vascular beds, where binding of *dopamine* produces vasodilation. D2  
receptors are also found on presynaptic adrenergic neurons, where  
their activation interferes with *norepinephrine* release.  
 *Actions*  
 *Cardiovascular:* *Dopamine* exerts a stimulatory effect on the  
beta receptors of the heart, having both positive inotropic and  
chronotropic effects. At very high doses, *dopamine* activates alfa1 receptors on the vasculature, resulting in vasoconstriction.

*Renal and visceral:*

*Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera. These receptors are not affected by alfa- or beta-blocking drugs, and in the past, low-dose ("renal-dose") *dopamine* was often used in the prevention or treatment of  
acute renal failure. However, more recent data suggest there is  
limited clinical utility in the renal protective effects of *dopamine.  
Therapeutic uses:* *Dopamine* can be used for cardiogenic and  
septic shock and is given by continuous infusion. It raises blood pressure by stimulating the beta1 receptors on the heart to increase cardiac  
output, and alfa1 receptors on blood vessels to increase total peripheral  
resistance. It enhances perfusion to the kidney and splanchnic areas,  
as described above. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. By contrast, *norepinephrine* can diminish blood supply to the kidney and may reduce renal function. *Dopamine* is also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.  
*Adverse effects:*An overdose of *dopamine* produces the same  
effects as sympathetic stimulation. *Dopamine* is rapidly metabolized by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short lived.

***Oxymetazoline*** is a direct-acting synthetic adrenergic agonist that stimulates both alfa1- and alfa2- adrenergic receptors. *Oxymetazoline* is found in many over-the-counter nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses.  
*Oxymetazoline* directly stimulates *a* receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. It is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. Local irritation and sneezing may occur with intranasal administration. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

***Clonidine*** is an alfa2 agonist used for the treatment  
of hypertension. It can also be used to minimize symptoms of withdrawal from opiates, tobacco smoking, and benzodiazepines. Both *clonidine* and the ~ agonist *guanfacine* may be used in the management of attention deficit hyperactivity disorder. *Clonidine* acts centrally on presynaptic alfa2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are lethargy, sedation, constipation, and xerostomia. Abrupt discontinuation must be avoided to prevent rebound hypertension.

***Salmeterol, formoterol, and indacaterol***are long-acting beta2 selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol.* Unlike *formoterol,* however, *salmeterol* has a somewhat delayed onset of action. LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthma related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.

***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***  
The marked central stimulatory action of *amphetamine* is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by alfa1 agonist action on the vasculature, as well as bea1 stimulatory effects on the heart. Its actions are mediated primarily through an increase  
in non vesicular release of catecholamines such as dopamine and  
norepinephrine from nerve terminals. Thus, *amphetamine* is an  
indirect-acting adrenergic drug.

***Cocaine*** is unique among local anesthetics in having  
the ability to block the sodium-chloride (Na+/CI-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine.* In addition, the duration of action of epinephrine and norepinephrine is increased. Like *amphetamines,* it can increase blood pressure by alfa1 agonist actions and beta stimulatory effects.

***MIXED-ACTION ADRENERGIC AGONISTS***

***Ephedrine* and *pseudoephedrine***are mixed-action adrenergic agents. They not only enhance release of stored norepinephrine from nerve endings but also  
directly stimulate both alfa and beta receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine,* although  
less potent. *Ephedrine* and *pseudoephedrine* are not catecholamines  
and are poor substrates for COMT and MAO. Therefore, these drugs  
have a long duration of action. *Ephedrine* and *pseudoephedrine* have  
excellent absorption after oral administration and penetrate the CNS,  
but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated  
largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and it is indicated in anesthesia-induced hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol.* It was previously  
used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. Oral *pseudoephedrine* is primarily used to treat nasal and sinus congestion.

***CHARACTERISTICS OF 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 or exogenous agonists. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for alfa or beta receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

***alfa-ADRENERGIC BLOCKING AGENTS***

alfa-Adrenergic blocking agents antagonize the subtype(s) of alfa-adrenergic receptors (alfa1 or alfa2), depending on the specificity of the agent for the receptor subtype(s). Drugs that block a1-adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on alfa1 adrenoreceptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This lowered blood pressure induces reflex tachycardia. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. Selective alfa2 -adrenergic blockers have limited clinical utility.

***Phenoxybenzamine*** is a nonselective, non competitive blocker of alfa1 and alfa2-adrenergic receptors.

*Actions. Cardiovascular effects:* The drug prevents alfa receptor vasoconstriction of peripheral blood vessels caused by endogenous catecholamines, which leads to decreased peripheral resistance and resultant reflex tachycardia. However, by blocking presynaptic alfa2 receptors on the sympathetic nerve terminals in the heart, *phenoxybenzamine* causes an increase in the release of norepinephrine, which in turn increases heart rate and cardiac output (mediated by beta1 receptors). This may also lead to cardiac arrhythmias and anginal pain. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

*Epinephrine reversal:* All a-adrenergic blockers reverse the a agonist actions of *epinephrine.* For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of beta2 receptors is not blocked. Therefore, in the presence of *phenoxybenzamine,* the systemic blood pressure decreases in response to *epinephrine*.

*Therapeutic uses:* *Phenoxybenzamine* is used in the treatment of sweating and hypertension associated with pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. *Phenoxybenzamine* is sometimes effective in treating Raynaud disease and frostbite.

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

***Phentolamine:***In contrast to *phenoxybenzamine, phentolamine* produces a competitive block of alfa1and alfa2- receptors. Effects last for approximately 4 hours after a single injection. Pharmacological effects of *phentolamine* are very similar to those of *phenoxybenzamine.* It is used for the diagnosis and short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis following extravasation of *norepinephrine. Phentolamine* is useful to treat hypertensive crisis due to abrupt withdrawal of *clonidine* or ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors.

***Prazosin, terazosin, and doxazosin*** are selective competitive blockers of the alfa1 receptor. In contrast to *phenoxybenzamine* and *phentolamine,* they are useful in the treatment of hypertension. [Note: *Tamsulosin*, *alfuzosin*, and *silodosin* are examples of other selective alfa1 antagonists indicated for the treatment of benign prostatic hyperplasia]. Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin,* which appear in feces. *Doxazosin* is the longest acting of these drugs. *Mechanism of action:*These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. Unlike *phenoxybenzamine* and *phentolamine,* these drugs cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

*Therapeutic uses:*Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives, alfa1 antagonists are not used as monotherapy for the treatment of hypertension.

*Adverse effects:*alfa1- Blockers such as *prazosin* and *doxazosin* may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine).* An additive antihypertensive effect occurs when alfa1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors.

*Yohimbine*

*Yohimbine* is a selective competitive alfa2-blocker that works at the level of the CNS to increase sympathetic outflow to the periphery. It is found as a component of the bark of the yohimbe tree *(Pausinystalia yohimbe)* and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.

***Beta -ADRENERGIC BLOCKING AGENTS***

All of the clinically available beta-blockers are competitive antagonists. Nonselective beta-blockers act at both beta1 and beta2 receptors, whereas cardioselective beta antagonists primarily block b1 receptors. These drugs also differ in intrinsic sympathomimetic activity (ISA), CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics. Although all beta-blockers lower blood pressure, they do not induce postural hypotension, because the alfa-adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. Beta-Biockers are effective in treating systemic as well as portal hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma.

***Propranolol*** *is* a nonselective beta antagonist Propranolol is the prototype beta-adrenergic antagonist and blocks both beta1 and beta2 receptors with equal affinity. Sustained release preparations for once-a-day dosing are available. Nonselective  
beta-blockers, including propranolol, have the ability to block the actions  
of isoproterenol (beta1 and beta 2) on the cardiovascular system. Thus, in  
the presence of a beta-blocker, isoproterenol does not produce cardiac  
stimulation (beta1 mediated) or reductions in mean arterial pressure and  
diastolic pressure (beta2 mediated). [Note: In the presence  
of a nonselective beta-blocker, epinephrine no longer lowers diastolic  
blood pressure or stimulates the heart, but its vasoconstrictive action  
(mediated by alfa receptors) remains unimpaired. The actions of norepinephrine on the cardiovascular system are mediated primarily by alfa  
receptors and are, therefore, mostly unaffected.]  
*Actions*  
*Cardiovascular:* Propranolol diminishes cardiac output, having both negative inotropic and chronotropic effects. It directly depresses sinoatrial and atrioventricular nodal activity. The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, beta-blockers attenuate the expected increase in  
heart rate. Cardiac output, workload, and oxygen consumption  
are decreased by blockade of beta1 receptors, and these effects  
are useful in the treatment of angina. The beta-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).  
*Peripheral vasoconstriction:* Nonselective blockade of beta-receptors prevents beta2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance. The reduction in cardiac output produced by all beta-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total  
peripheral resistance returns to normal or decreases with long-term use of propranolol as a result of down regulation of the beta receptors. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

*Bronchoconstriction:* Blocking beta2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle. This can precipitate an  
exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, beta-blockers, particularly nonselective ones, are contraindicated in patients with asthma and should be avoided in COPD.  
*Disturbances in glucose metabolism:* beta-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if *propranolol* is given to a diabetic patient receiving *insulin,* careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after *insulin*injection. beta-Blockers also attenuate the normal physiologic  
response to hypoglycemia.

*Therapeutic uses*

*Hypertension:* *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism,  
but inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects.

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

*Myocardial infarction:* *Propranolol* and other beta-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction seem to be protected against a second heart attack by prophylactic use of beta-blockers. In addition, administration of a beta-blocker immediately following a myocardial infarction reduces infarct size and early mortality. The mechanism for these effects may be a reduction in the actions of circulating catecholamines that increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

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

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

*Adverse effects*

*Bronchoconstriction:**Propranolol* has the potential to cause significant bronchoconstriction due to blockade of beta2 receptors. Death by asphyxiation has been reported for patients with asthma who inadvertently received the drug.  
Therefore, *propranolol* is contraindicated in patients with COPD or asthma.  
*Arrhythmias:* Treatment with beta-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The beta-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a beta antagonist leads to up-regulation of the beta-receptor. On suspension of therapy, the increased receptors can precipitate worsened angina or hypertension through action of endogenous catecholamines on the up-regulated beta-receptors; *sexual impairment; metabolic disturbances; CNS effects.*

*Drug interactions:* Drugs that interfere with, or inhibit, the metabolism of *propranolol,* such as *cimetidine, fluoxetine, paroxetine,* and *ritonavir,* may potentiate its antihypertensive effects. Conversely, those that stimulate or induce its  
metabolism, such as barbiturates, *phenytoin,* and *rifampin,* can decrease its effects. Nonselective beta-blockers such as *propranolol* may prevent the rescue effects of *epinephrine* in anaphylaxis.

***Nadolol and timolol:*** nonselective beta-antagonists *Nadolol* and *timolol* also block beta1 and beta2-adrenoceptors and are more potent than *propranolol. Nadolol* has a very long duration of action. *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma.

***Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: selective beta1 antagonists***

Drugs that preferentially block the beta1 receptors minimize the unwanted  
bronchoconstriction (beta2 effect) seen with use of nonselective agents  
in asthma patients. Cardioselective beta-blockers, such as *acebutolol*, *atenolol*, and *metoprolol*, antagonize beta1 receptors at doses 50- to 100-fold less than those required to block *beta2* receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses.

*Actions:* These drugs lower blood pressure in hypertension and  
increase exercise tolerance in angina. *Esmolol* has a very short half-life due to metabolism of an ester linkage. It is only available intravenously and is used to  
control blood pressure or heart rhythm in critically ill patients and those undergoing surgery or diagnostic procedures. In addition to its cardioselective beta-blockade, *nebivolol* releases nitric oxide from endothelial cells and causes vasodilation. In contrast to *propranolol,* the cardioselective beta-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must  
be carefully monitored to make certain that respiratory activity is not  
compromised. Because these drugs have less effect on peripheral  
vascular beta2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of beta-blockers, is less frequent.

*Therapeutic uses:* The cardioselective beta-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina. *Bisoprolol* and the extended-release formulation of *metoprolol* are indicated for the management of chronic heart failure.

***Acebutolol and pindolol: antagonists with partial agonist activity***

*Actions*  
*Cardiovascular:* *Acebutolol* (beta1-selective antagonist) and *pindolol* (nonselective beta-blocker) are not pure antagonists. These drugs can also weakly stimulate both beta1 and beta2 receptors and are said to have ISA (Intrinsic sympathomimetic activity). These partial agonists stimulate the beta receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on reduction of cardiac rate and cardiac output compared to that of beta-blockers without ISA.

*Decreased metabolic effects:* beta-Blockers with ISA minimize  
the disturbances of lipid and carbohydrate metabolism that are seen with other beta-blockers. For example, these agents do not decrease plasma HDL levels. *Therapeutic use:* beta-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs.

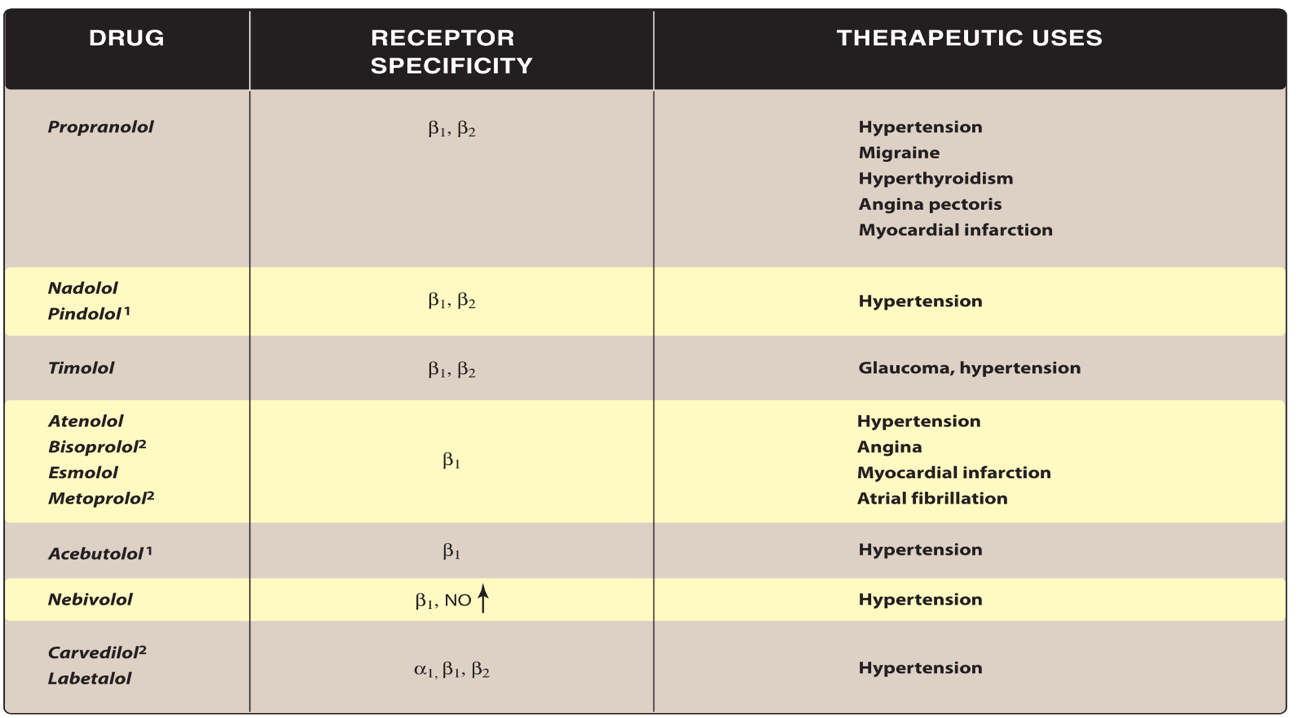
***Labetalol and carvedilol:*** *antagonists of both alfa- and beta-adrenoceptors*

*Actions:* *Labetalol* and *carvedilol* are nonselective beta-blockers with concurrent alfa1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other beta-blockers that produce initial  
peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

*Therapeutic use in hypertension and heart failure:*

*Labetalol* is used as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure. Beta-Blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, *carvedilol* as well as *metoprolol* and *bisoprolol* are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time. *Adverse effects:* Orthostatic hypotension and dizziness are  
associated with alfa1-blockade.

***Summary table*** ***of beta-adrenergic antagonists.*** *Acebutolol*, and *pindolol* are partial agonists. *Bisoprolol,* *metoprolol,* and *carvedilol* are also used for the treatment of heart failure.

****

***DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE***

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the  
neurotransmitter into the adrenergic neuron. However, due to the advent  
of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. ***Reserpine*** is one of the remaining agents in this category. *Reserpine,* a plant alkaloid, blocks the Mg2+/adenosine triphosphatedependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. *Reserpine* has a slow onset, a long duration of action, and effects that persist for many days after discontinuation. It has been used for the management of hypertension but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions. It is also indicated in agitated psychotic states such as schizophrenia to relieve symptoms.