Lecture 4 Dr. Haedar

The Adrenergic Neuron

Adrenergic neurons release norepinephrine as the primary neurotransmitter.

Adrenergic receptors

α_1 and α_2 Receptors: The α-adrenoceptors show a weak response to the synthetic agonist isoproterenol, but they are responsive to the naturally occurring catecholamines epinephrine and norepinephrine. For α receptors, the rank order of potency is epinephrine ≥ norepinephrine >> isoproterenol. The α-adrenoceptors are subdivided into two subgroups, α_1 and α_2, based on their affinities for α agonists and blocking drugs

α_1 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.

α_2 Receptors: These receptors, located primarily on presynaptic nerve endings and on other cells, such as the β cell of the pancreas, and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released norepinephrine traverses the synaptic cleft and interacts with the α_1 receptors. A portion of the released norepinephrine "circles back" and reacts with α_2 receptors on the neuronal membrane. The stimulation of the α_2 receptor causes feedback inhibition of the ongoing release of norepinephrine from the stimulated adrenergic neuron.

Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, α_{2C}, and α_{2D}. This extended classification is necessary for understanding the selectivity of some drugs. For example, tamsulosin is a selective α_{1A} antagonist that is used to treat benign prostate hyperplasia. The drug is clinically useful because it targets α_{1A} receptors found primarily in the urinary tract and prostate gland.

β Receptors: These are characterized by a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine. For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists, although several others have been identified by gene cloning. [It is known that β_3 receptors are involved in lipolysis but their role in other specific reactions are not known] . β_1 Receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β_2 receptors have a higher affinity for epinephrine than for norepinephrine.

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 decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase A or β-adrenergic receptor kinase.

A. Effects of Alpha 1 -Receptor Activation

Alpha 1 receptors are widely expressed in vascular beds, and their activation leads to arterial and venous vasoconstriction. Their direct effect on cardiac function is of relatively less importance. A relatively pure α agonist such as phenylephrine increases peripheral arterial resistance and decreases venous capacitance. The enhanced arterial resistance usually leads to a dose-dependent rise in blood pressure.

Effects of Alpha 2 -Receptor Activation

Alpha 2 adrenoceptors are present in the vasculature, and their activation leads to vasoconstriction. This effect, however, is observed only when α 2 agonists are given

locally, by rapid intravenous injection or in very high oral doses. When given systemically, these vascular effects are obscured by the central effects of α 2 receptors,

Which lead to inhibition of sympathetic tone and blood pressure. Hence, α 2 agonists are used as sympatholytics in the treatment of hypertension. In patients with pure autonomic failure, characterized by neural degeneration of postganglionic noradrenergic fibers, clonidine may increase blood pressure because the central sympatholytic effects of clonidine become irrelevant, whereas the peripheral vasoconstriction remains intact.

Effects of Beta-Receptor Activation

The blood pressure response to a β-adrenoceptor agonist depends on its contrasting effects on the heart and the vasculature. Stimulation of β receptors in the heart increases cardiac output by increasing contractility and by direct activation of the sinus node to increase heart rate. Beta agonists also decrease peripheral resistance by activating β 2 receptors, leading to vasodilation in certain vascular beds.

Effects of Dopamine-Receptor Activation

Intravenous administration of dopamine promotes vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels, via activation of D 1 receptors. Activation of the D 1 receptors in the renal vasculature may also induce natriuresis. The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output). The activation of presynaptic D 2 receptors suppresses norepinephrine release, but it is unclear if this contributes to cardiovascular effects of dopamine. In addition, dopamine activates β 1 receptors in the heart. At low doses, peripheral resistance may decrease. At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed. Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

Non-cardiac Effects of Sympathomimetics

Activation of β 2 receptors in **bronchial smooth muscle** leads to bronchodilation.

In the **eye,** α receptors activation by drugs such as phenylephrine causes mydriasis. Alpha stimulants also have important effects on intraocular pressure. Alpha agonists increase the

outflow of aqueous humor from the eye and can be used clinically to reduce intraocular pressure. In contrast, β agonists have little effect, but β antagonists decrease the production of aqueous humor. These effects are important in the treatment of glaucoma. In **genitourinary** organs, the bladder base, urethral sphincter and prostate contain α receptors that mediate contraction and therefore promote urinary continence. The **salivary glands** contain adrenoceptors that regulate the secretion of amylase and water. However, certain sympathomimetic drugs, eg, clonidine, produce symptoms of dry mouth. The **apocrine sweat glands,** located on the palms of the hands and a few other areas, respond to adrenoceptor stimulants with increased sweat production. These are the apocrine non-thermoregulatory glands usually associated with psychological stress. **metabolism.** Activation of β adrenoceptors in fat cells leads to increased lipolysis with enhanced release of free fatty acids and glycerol into the blood. Beta 3 adrenoceptors play a role in mediating this response in animals, but their role in humans is probably minor. Sympathomimetic drugs enhance glycogenolysis in the liver, which leads to increased glucose release into the circulation. In the human liver, the effects of catecholamines are probably mediated mainly by β receptors, though α 1 receptors may also play a role. Catecholamines in high concentration may also cause metabolic acidosis. Activation of β 2 adrenoceptors by endogenous epinephrine or by sympathomimetic drugs promotes the uptake of potassium into cells, leading to a fall in extracellular potassium. This may result in a fall in the plasma potassium concentration during stress or protect against a rise in plasma potassium during exercise.

SPECIFIC SYMPATHOMIMETIC DRUGS

Endogenous Catecholamines

Epinephrine (adrenaline) is an agonist at both α and β receptors. It is therefore a very potent vasoconstrictor and cardiac stimulant. The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly β 1 receptors) and the vasoconstriction induced in many vascular beds (α receptors). Epinephrine also activates β 2 receptors in some vessels (eg, skeletal muscle blood vessels), leading to their dilation. Consequently,

total peripheral resistance may actually fall, explaining the fall in diastolic pressure that is sometimes seen with epinephrine injection. Activation of β 2 receptors in skeletal muscle contributes to increased blood flow during exercise.

Norepinephrine is an agonist at both α 1 and α 2 receptors. Norepinephrine also activates β 1 receptors with similar potency as epinephrine, but has relatively little effect on β 2 receptors. Consequently, norepinephrine increases peripheral resistance and both diastolic and systolic blood pressure. Compensatory baroreflex activation tends to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained.

Dopamine is the immediate precursor in the synthesis of norepinephrine . Endogenous dopamine may have more important effects in regulating sodium excretion and renal function. It is an important neurotransmitter in the central nervous system and is involved in the reward stimulus relevant to addiction. Its deficiency in the basal ganglia leads to Parkinson's disease, which is treated with its precursor levodopa. Dopamine receptors are also targets for antipsychotic drugs.

Direct-Acting Sympathomimetics

Phenylephrine Because it is not a catechol derivative ,it is not inactivated by COMT and has a longer duration of action than the catecholamines. It is an effective mydriatic and decongestant and can be used to raise the blood pressure.

Methoxamine acts pharmacologically like phenylephrine, since it is predominantly a direct-acting α 1 -receptor agonist. It may cause a prolonged increase in blood pressure due to vasoconstriction; it also causes a vagally mediated bradycardia. Methoxamine is available for parenteral use, but clinical applications are rare and limited to hypotensive states.

Alpha 2 - selective agonists have an important ability to decrease blood pressure through actions in the central nervous system even though direct application to a blood vessel may cause vasoconstriction. Such drugs (eg, **clonidine, methyldopa, guanfacine, guanabenz**) are useful in the treatment of hypertension . On the other hand, the primary indication of **dexmedetomidine** is for sedation of initially intubated and mechanically ventilated patients

during treatment in an intensive care setting. It also reduces the requirements for opioids in pain control. Finally, **tizanidine** is used as a central muscle relaxant.

Xylometazoline and **oxymetazoline** are direct-acting α agonists. These drugs have been used as topical decongestants because of their ability to promote constriction of the nasal mucosa. When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect. Oxymetazoline has significant affinity for α 2A receptors.

Isoproterenol (isoprenaline) is a very potent β-receptor agonist and has little effect on α receptors. The drug has positive chronotropic and inotropic actions; because isoproterenol activates β receptors almost exclusively, it is a potent vasodilator. These actions lead to a marked increase in cardiac output associated with a fall in diastolic and mean arterial pressure and a lesser decrease or a slight increase in systolic pressure

Beta-selective agonists :- Beta 1 -selective agents include **dobutamine** and a partial agonist, **prenalterol**. Because they are less effective in activating vasodilator β 2 receptors, they may increase cardiac output with less reflex tachycardia than occurs with nonselective β agonists such as isoproterenol. **Dobutamine** was initially considered a relatively β 1 -selective agonist, but its actions are more complex. Its chemical structure resembles dopamine, but its actions are mediated mostly by activation of α and β receptors. Dobutamine has a positive inotropic action caused by the isomer with predominantly β-receptor activity. It has relatively greater inotropic than chronotropic effect compared with isoproterenol.

Mixed-Acting Sympathomimetics

Ephedrine and pseudoephedrine

Ephedrine and *pseudoephedrine* are plant alkaloids, that are now made synthetically. These drugs are mixed-action adrenergic agents. They not only release 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* and *pseudoephedrine* are not catechols and are poor substrates for COMT and

MAO; thus, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS; however, *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in the urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in the urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. *Ephedrine* produces bronchodilation, but it is less potent than *epinephrine* or *isoproterenol* in this regard and produces its action more slowly. It is therefore sometimes used prophylactically in chronic treatment of asthma to prevent attacks rather than to treat the acute attack. *Ephedrine* enhances contractility and improves motor function in myasthenia gravis, particularly when used in conjunction with anticholinesterases. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. *Ephedrine* has been used to treat asthma, as a nasal decongestant (due to its local vasoconstrictor action), and to raise blood pressure. *Pseudoephedrine* is primarily used to treat nasal and sinus congestion or congestion of the eustachian tubes

Indirect-Acting Sympathomimetics

A. Amphetamine-Like

Amphetamine even more readily enters the central nervous system, where it has marked stimulant effects on mood and alertness and a depressant effect on appetite. Its D-isomer is more potent than the L-isomer. Amphetamine's actions are mediated through the release of norepinephrine and, to some extent, dopamine.

Methamphetamine is very similar to amphetamine with an even higher ratio of central to peripheral actions. **Phenmetrazine** is a variant phenylisopropylamine with amphetamine-like effects. It has been promoted as an anorexiant and is also a popular drug of abuse. **Methylphenidate** is an amphetamine variant whose major pharmacologic effects and abuse potential are similar to those of amphetamine. Methylphenidate may be effective in some children with attention deficit hyperactivity disorder

Modafinil is a psychostimulant . Its mechanism of action is not fully known. It inhibits both norepinephrine and dopamine transporters, and it increases synaptic concentrations not only of norepinephrine and dopamine, but also of serotonin and glutamate, while decreasing GABA levels. It is used primarily to improve wakefulness in narcolepsy and some other conditions. It is often associated with increases in blood pressure and heart rate, though these are usually mild .

Tyramine If administered parenterally, it has an indirect sympathomimetic action caused by the release of stored catecholamines. Consequently, tyramine's spectrum of action is similar to that of norepinephrine. In patients treated with MAO inhibitors—particularly inhibitors of the MAO-A isoform—this effect of tyramine may be greatly intensified, leading to marked increases in blood pressure. This occurs because of increased bioavailability of tyramine and increased neuronal stores of catecholamines. Patients taking MAO inhibitors must be very careful to avoid tyramine-containing foods.

B. Catecholamine Reuptake Inhibitors

Many inhibitors of the amine transporters for norepinephrine, dopamine, and serotonin are used clinically. Although specificity is not absolute, some are highly selective for one of the transporters. Many antidepressants, particularly the older tricyclic antidepressants, can inhibit norepinephrine and serotonin reuptake to different degrees. This may lead to orthostatic tachycardia as a side effect. Some antidepressants of this class, particularly imipramine, can induce orthostatic hypotension presumably by their clonidine-like effect or by blocking α 1 receptors, but the mechanism remains unclear.

Atomoxetine is a selective inhibitor of the norepinephrine reuptake transporter. Its actions, therefore, are mediated by potentiation of norepinephrine levels in noradrenergic synapses. It is used in the treatment of attention deficit disorders. **Reboxetine** has similar characteristics as atomoxetine. **Sibutramine** is a serotonin and norepinephrine reuptake inhibitor and was initially approved by the FDA as an appetite suppressant for long-term treatment of obesity. It has been taken off the market in the United States and several other countries because it has been associated with a small increase in cardiovascular events including strokes in patients with a history of cardiovascular disease, which outweighed the

benefits gained by modest weight reduction. **Duloxetine** is a widely used antidepressant with balanced serotonin and norepinephrine reuptake inhibitory effects .**Cocaine** is a local anesthetic with a peripheral sympathomimetic action that results from inhibition of transmitter reuptake at noradrenergic synapses .

Albuterol, pirbuterol, and terbutaline

Albuterol, *pirbuterol*, and *terbutaline* are short-acting β_2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. Compared with the nonselective β-adrenergic agonists, such as *metaproterenol*, these drugs produce equivalent bronchodilation with less cardiac stimulation.

Salmeterol and formoterol

Salmeterol and *formoterol* are β_2-adrenergic selective, long-acting bronchodilators. 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. These agents are not recommended as monotherapy and are highly efficacious when combined with a corticorsteroid. *Salmeterol* and *formoterol* are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

Adrenergic Antagonists

α-Adrenergic Blocking Agents

Drugs that block α-adrenoceptors profoundly affect blood pressure.

A. Phenoxybenzamine

Phenoxybenzamine is nonselective, linking covalently to both α_1-postsynaptic and α_2-presynaptic receptors. The block is irreversible and noncompetitive.

Actions:

Cardiovascular effects: By blocking α receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia.Furthermore, the ability to block presynaptic inhibitory α_2 receptors in the heart can contribute to an increased cardiac output. **Epinephrine reversal:** All α-adrenergic blockers reverse the α-agonist actions of *epinephrine*. **Therapeutic uses:** *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with *phenoxybenzamine* to preclude the hypertensive crisis that can result from manipulation of the tissue. Autonomic hyperreflexia, which predisposes paraplegics to strokes, can be managed with *phenoxybenzamine*.**Adverse effects:** *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It can inhibit ejaculation. The drug also may induce reflex tachycardia, mediated by the baroreceptor reflex, and is contraindicated in patients with decreased coronary perfusion.

Phentolamine

In contrast to *phenoxybenzamine, phentolamine* produces a competitive block of α_1 and α_2 receptors. The drug's action lasts for approximately 4 hours after a single administration. Like *phenoxybenzamine*, it produces postural hypotension and causes *epinephrine* reversal.The drug can also trigger arrhythmias and anginal pain, and it is contraindicated in patients with decreased coronary perfusion. *Phentolamine* is also used for the short-term management of pheochromocytoma.

Prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin

Prazosin, *terazosin*, *doxazosin*, and *tamsulosin* are selective competitive blockers of the α_1 receptor. the first three drugs are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* are indicated for the treatment of benign prostatic hypertrophy (also known as benign prostatic hyperplasia or BPH). **Cardiovascular effects:** All of these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. *Tamsulosin* has the least effect on blood pressure. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and the glomerular filtration rate.

Therapeutic uses: Individuals with elevated blood pressure who have been treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs produces 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. An increase in the risk of congestive heart failure has been reported when α_1-receptor blockers have been used as monotherapy in hypertension. The α_1-receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH. Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. *Tamsulosin* is a more potent inhibitor of the α_{1A} receptors found on the smooth muscle of the prostate. **Adverse effects:** α_1 Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension Due to a tendency to retain sodium and fluid, *prazosin* is frequently used along with a diuretic.

D. Yohimbine

Yohimbine is a selective competitive α_2 blocker. It is found as a component of the bark of the yohimbe tree and is sometimes used as a sexual stimulant. *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery. It directly blocks α_2 receptors and has been used to relieve vasoconstriction associated with Raynaud's disease.

β-Adrenergic Blocking Agents

All the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors

Propranolol: A nonselective β antagonist

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

Actions:Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects. It directly depresses sinoatrial and atrioventricular activity. The resulting bradycardia usually limits the dose of the drug. Cardiac output, work, and oxygen consumption are decreased by blockade of β_1 receptors; these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias but generally are not effective against ventricular arrhythmias (except those induced by exercise).

Peripheral vasoconstriction: Blockade of β receptors prevents β_2-mediated vasodilation. The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. On balance, there is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, because the α_1-adrenergic receptors that control vascular resistance are

unaffected.**Bronchoconstriction:** Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle β-Blockers, and in particular nonselective ones, are thus contraindicated in patients with COPD or asthma.**Increased Na^+ retention:** Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume. **Disturbances in glucose metabolism:** β-blockade leads to decreased glycogenolysis and decreased glucagon secretion.

Blocked action of isoproterenol: All β-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* on the cardiovascular system.

Therapeutic effects Hypertension: *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 and decreased sympathetic outflow from the CNS also contribute to *propranolol's* antihypertensive effects **Glaucoma:** β-Blockers, particularly topically applied *timolol*, are effective in diminishing intraocular pressure in glaucoma.

Migraine: *Propranolol* is also effective in reducing migraine episodes when used prophylactically .**Hyperthyroidism:** *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.**Angina pectoris:** *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing the chest pain on exertion that is common in angina. Tolerance to moderate exercise is increased, and this is measurable by improvement in the electrocardiogram.

Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial

infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery. The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

Adverse effects: Bronchoconstriction: *Propranolol* has a serious and potentially lethal side effect when administered to an asthmatic .An immediate contraction of the bronchiolar smooth muscle prevents air from entering the lungs. Deaths by asphyxiation have been reported for asthmatics who were inadvertently administered the drug. Therefore, *propranolol* must never be used in treating any individual with COPD or asthma. **Arrhythmias:** Treatment with β-blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually for 1 week. Long-term treatment with a β antagonist leads to up-regulation of the β-receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension. **Sexual impairment:** Because sexual function in the male occurs through α-adrenergic activation, β-blockers do not affect normal ejaculation or the internal bladder sphincter function.

Disturbances in metabolism: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur

Drug interactions: Drugs that interfere with the metabolism of *propranolol*, such as *cimetidine, fluoxetine, paroxetine*, and *ritonavir*, may potentiate its antihypertensive effects. Conversely, those that stimulate its metabolism, such as barbiturates, *phenytoin,* and *rifampin*, can decrease its effects.

B. Timolol and nadolol: Nonselective β antagonists *Timolol* and *nadolol* also block β_1- and β_2- adrenoceptors and are more potent than *propranolol*. *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

C. Acebutolol, atenolol, metoprolol, and ,bisoprolol ,betaxolol,nebivolol and esmolol: Selective β_1 antagonists

Cardioselective β-blockers, such as *acebutolol* and *atenolol* and *metoprolol* antagonize β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors. This cardioselectivity is thus 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 lifetime due to metabolism of an ester linkage. It is only given intravenously if required during surgery or diagnostic procedures (for example, cystoscopy). In contrast to *propranolol*, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthmatics treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised.**Therapeutic use in hypertension:** The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function. Because these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities, a common side effect of β-blocker therapy, is less frequent. Cardioselective β-blockers are useful in diabetic hypertensive patients who are receiving insulin or oral hypoglycemic agents.

Pindolol and acebutolol: Antagonists with partial agonist activity

Actions: Cardiovascular: *Acebutolol* and *pindolol* are not pure antagonists; instead, they have the ability to weakly stimulate both β_1

and β_2 receptors and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, *epinephrine* and norepinephrine.

Decreased metabolic effects: Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. **Therapeutic use in hypertension:** β-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with *acebutolol* and *pindolol* than it is with *propranolol*, making them valuable in the treatment of diabetics.

Labetalol and carvedilol and bisoprolol: Antagonists of both α- and β- adrenoceptors :-**Actions:** *Labetalol* , *carvedilol* and bisoprolol are reversible β-blockers with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce peripheral vasoconstriction, and they are therefore useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. They do not alter serum lipid or blood glucose levels. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.**Therapeutic use in hypertension:** *Labetalol* is useful for treating the elderly or black hypertensive patient in whom increased peripheral vascular resistance is undesirable. *Labetalol* may be employed as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. **Adverse effects:** Orthostatic hypotension and dizziness are associated with α_1 blockade.

some agonists, such as *amphetamine* and *tyramine*, do not act directly on the adrenoceptor. Instead, they exert their effects indirectly on the adrenergic neuron by causing the release of neurotransmitter from storage vesicles. Similarly, some agents act on the adrenergic neuron, either to interfere with neurotransmitter release or to alter the uptake of the neurotransmitter into the adrenergic nerve

A. Reserpine *Reserpine* a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphate–dependent transport of biogenic amines, norepinephrine, *dopamine*, and *serotonin* from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues.

Guanethidine

Guanethidine blocks the release of stored norepinephrine as well as displaces norepinephrine from storage vesicles (thus producing a transient increase in blood pressure). This leads to gradual depletion of norepinephrine in nerve endings except for those in the CNS. *Guanethidine* commonly causes orthostatic hypotension and interferes with male sexual function. Supersensitivity to norepinephrine due to depletion of the amine can result in hypertensive crisis in patients with pheochromocytoma.

Cocaine Although cocaine inhibits norepinephrine uptake, it is an adrenergic agonist.