SYMPATHOLYTICS

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ADRENOCEPTOR ANTAGONISTS

Adrenoceptor antagonists can block α-adrenoceptors, β-adrenoceptors, or both.

Adrenoceptor Antagonists

- The therapeutic effects are caused primarily by blockade of α_1- or β_1-adrenoceptors, whereas the adverse effects tend to be related to blockade of α_2- or β_2-adrenoceptors.
- Drugs that selectively block either α_1- or β_1-adrenoceptors have been developed in an effort to avoid the adverse effects caused by α_2- or β_2-adrenoceptor blockade.

- Blockade of α_1-adrenoceptors relaxes vascular and whereas blockade of β_1-adrenoceptors reduces sympathetic stimulation of the heart.

α-Adrenoceptor Antagonists

Nonselective α-blockers

- Phenoxybenzamine
- Phentolamine

Selective α1-blockers

- Doxazosin
- Tamsulosin
- Alfuzosin

β-Adrenoceptor Antagonists

Nonselective β-blockers

- Propranolol
- Timolol
- Pindolol

Selective β1-blockers

- Atenolol
- Metoprolol

α- and β-Adrenoceptor Antagonists

- Carvedilol
- Labetalol

TABLE 9.1 Responses to Adrenergic and Cholinergic Nerve Stimulation

Organ or Tissue Function	Predominant Adrenoceptor Type	Adrenergic Response	Cholinergic Response[a]
Heart[b]			
Rate (chronotropic effect)	β_1	Increase	Decrease
Contractile force (inotropic effect)	β_1	Increase	None
Conduction velocity (dromotropic effect)	β_1	Increase	Decrease
Eye			
Pupil size	α_1	Constriction of radial muscle causing dilation (mydriasis)	Contraction of circular muscle (miosis)
Accommodation		No innervation	Contraction of ciliary muscle producing accommodation for near vision
Bronchial smooth muscle	β_2	Relaxation	Contraction
Blood vessels (arteries and arterioles)[c]			
Cutaneous	α_1	Constriction	No innervation[e]
Visceral	α_1	Constriction	No innervation[e]
Pulmonary	α_1	Constriction	No innervation[e]
Skeletal muscle	α_1, β_2	Constriction[d]	No innervation[e]
Coronary	α_1, β	Constriction, dilation[f]	No innervation[e]
Cerebral	α_1	Constriction	
Veins	α_1	Constriction	No innervation
Gastrointestinal tract (tone, motility, and secretory activity)	α_2, β_2	Decrease[g]	Increase
Sphincters	α	Contraction	Relaxation
Splenic capsule	α_1	Contraction	No innervation
Urinary bladder			
Detrusor muscle	β	Relaxation	Contraction
Trigone-sphincter muscle	α_1	Contraction	Relaxation
Uterus	α_1, β_2	Contraction-relaxation[h]	Contraction-relaxation
Glycogenolysis			
Skeletal muscle	β_2	Increase	None
Liver	α_1, β_2	Increase	None
Lipolysis	β_1	Increase	None
Renin secretion	β_1	Increase	None
Insulin secretion	α_2	Decrease	Increase

Nonselective α-Blockers

- Phenoxybenzamine and phentolamine are examples.
- **Phenoxybenzamine** is a noncompetitive antagonist, whereas **phentolamine** is a competitive adrenoceptor antagonist.
- Phenoxybenzamine undergoes spontaneous chemical transformation in the body to an active metabolite that forms a stable covalent bond with the α-adrenoceptor, resulting in a noncompetitive antagonism of epinephrine and other adrenoceptor agonists

- The drug has a duration of action of 3 to 4 days because of its stable covalent bonding with α-adrenoceptors.
- Phenoxybenzamine is used to treat **hypertensive episodes in patients** with **pheochromocytoma.**

Nonselective α-Blockers

- Phenoxybenzamine has been used to control hypertension until surgery can be performed to remove the tumor
- **Phentolamine** is a competitive adrenoceptor antagonist that produces vasodilation, decreases peripheral vascular resistance, and decreases blood pressure.
- After intravenous administration of phentolamine, the onset of action is immediate, and the duration of action is 10 to 15 minutes.

- After intramuscular or subcutaneous administration, the onset of action is 15 to 20 minutes, and the duration is 3 to 4 hours. The drug is metabolized chiefly in the liver before excretion in the urine.
- It is used in the treatment of **hypertensive episodes caused by α-adrenoceptor agonists.**

Nonselective α-Blockers

- **In addition, it is used** to treat **dermal necrosis and ischemia caused by extravasation or accidental injection of** epinephrine or other vasopressor amines

- Phentolamine and other nonselective α-blockers are not useful in treating hypertension, partly because they evoke reflex tachycardia and cause dizziness, headache, and nasal congestion.

Selective α_1-Blockers

- The selective α_1-blockers relax vascular and other smooth muscles, including those of the urinary bladder, urethra, and prostate.
- Because they produce vasodilation and decrease blood pressure, they are used to treat essential (primary) hypertension.

- The selective α_1-blockers do not cause as much reflex tachycardia as do nonselective blockers (block both α_1- and α_2-adrenoceptors).
- Blockade of α_2- adrenoceptors on sympathetic neurons prevents feedback inhibition of norepinephrine release and thereby leads to increased activation of cardiac β_1-adrenoceptors and tachycardia

Selective α_1-Blockers

- The selective α_1-blockers are quite useful in treating **lower** urinary tract symptoms associated with benign prostatic hyperplasia and other conditions.
- The α_1-blockers cause relaxation of prostatic and urethral smooth muscle due to blockade of α_1-receptors in these tissues leading to relief of lower urinary tract symptoms

- The most common adverse effects of α_1-blockers include hypotension, dizziness, and sedation, and these effects due to excessive vasodilation as well as to the central nervous system effects of these drugs
- A small percentage of men experience abnormal ejaculation when taking α_1-blockers.

Selective α_1-Blockers

- **Prazosin**, half-life is shorter than that of other α_1-antagonists, has a duration of action of about 6 hours.
- **Doxazosin and terazosin** are longer acting α_1-blockers that are usually administered once a day to treat hypertension or to relieve lower urinary tract symptoms.

- Their duration of action ranges from about 20 hours (terazosin) to about 30 hours (doxazosin).

- **Alfuzosin and tamsulosin** are more uroselective α_1-blockers that relieve lower urinary tract symptoms without causing as much hypotension, dizziness, and sedation as other α_1-blockers

Non-Selective β- adrenoceptor blockers

- Examples include nadolol, pindolol, propranolol, timolol.
- In addition to blocking β1-adrenoceptors in heart tissue, they block β2-adrenoceptors in smooth muscle, liver,

  and other tissues
- The non-selective β-blockers competitively block the effects of norepinephrine and other adrenoceptor agonists at β_1- and β_2-adrenoceptors.

- In addition, some of them exhibit intrinsic sympathomimetic **(Pindolol)** activity and membrane-stabilizing (local anesthetic) activity (Propranolol).
- Blockade of β_1-adrenoceptors reduces sympathetic stimulation of the heart and thereby produces a negative chronotropic, inotropic, and dromotropic effect.

Non-Selective β- adrenoceptor blockers

- Because the β-blockers reduce cardiac output and blood pressure, they can be used to treat arterial hypertension.
- In the kidneys, β_1-adrenoceptor blockade reduces the secretion of renin from the juxtaglomerular cells.
- In the eye, adrenoceptor blockade reduces aqueous humor secretion and intraocular pressure.

- Blockade of β_2-adrenoceptors produces several effects that can lead to adverse reactions in some patients receiving β-blockers, such as patients with asthma or diabetes.
- In the lungs, antagonism of β_2-adrenoceptors can cause bronchoconstriction in patients with asthma.

Non-Selective β- Adrenoceptor blockers

- In the liver, β2-adrenoceptor blockade inhibits epinephrine-stimulated glycogenolysis and can thereby slow the recovery of blood glucose after a hypoglycemic episode in a patient with diabetes.
- The β-blockers can also mask some of the early signs of hypoglycemia (e.g., tachycardia and sweating), which would otherwise alert the diabetic patient to this problem.

- For these reasons, β-blockers should be used cautiously in patients with diabetes and particularly in those who have insulin-dependent diabetes and are susceptible to hypoglycemic episodes associated with excessive insulin administration

Non-Selective β- Adrenoceptor blockers

- Of these four drugs, only pindolol has **intrinsic sympathomimetic activity, or partial agonist activity, which enables it to exert a weak agonist effect on β-adrenoceptors.**
- **This effect is** observed when the patient is resting and sympathetic tone is low, and it can result in a smaller

  reduction in heart rate than that caused by β-blockers without intrinsic sympathomimetic activity.

- When sympathetic tone is high, pindolol acts as a competitive receptor antagonist to inhibit sympathetic stimulation of the heart in the same manner as other β-blockers.

Timolol

- Timolol is administered orally to treat **hypertension, to reduce the risk of death in patients with acute myocardial infarction, and to prevent migraine headache.**
- **Timolol was the first β-blocker** to be used to treat **glaucoma and is available as an ophthalmic solution for topical ocular** administration.

- In glaucoma, β-blockers reduce aqueous humor secretion (by the cilliary body) and intraocular pressure.
- Timolol was selected for ophthalmic use partly because it does not have membrane-stabilizing activity and, therefore, does not anesthetize the cornea when instilled into the eye.

Clinical Uses of **Propranolol**

- **Hypertension,**
- **Anginapectoris, or**
- **Cardiac arrhythmias**
- **Hypertrophic subaortic stenosis (a form of hypertrophic cardiomyopathy,**
- **Essential tremor (a benign condition characterized by involuntary trembling of the** hands).
- Propranolol is also used to prevent **migraine headache**
- **As adjunctive therapy in the** treatment of **acute thyrotoxicosis, acute myocardial infarction, and pheochromocytoma.**

Selective β1-Blockers

- Include acebutolol, atenolol, esmolol, and metoprolol
- Because β_1-adrenoceptors are primarily located in cardiac tissue, the β_1-blockers are also known as **cardioselective β-blockers**
- In comparison with the nonselective β-blockers, the selective β_1-blockers produce less bronchoconstriction and, other β_2-adrenoceptor-mediated effects.

- Their selectivity for β_1-adrenoceptors, however, is not absolute, and β_2-receptor blockade increases with dosage.
- For this reason, selective β_1-blockers should be used with caution in patients who have asthma.

Selective β1-Blockers

- **Acebutolol** is a cardioselective β-blocker with a low degree of intrinsic sympathomimetic activity.
- It is converted to an active metabolite, **N-acetyl acebutolol, which has a longer half-life than the** parent compound and accounts for the drug's relatively long duration of action.

- **Atenolol** shows less variability in its oral absorption than do other β-blockers and is excreted largely unchanged in the urine.
- It also has lower lipid solubility and has been associated with a lower incidence of central nervous system side effects (e.g., vivid dreams, tiredness, and depression).

Selective β1-Blockers

- **Esmolol** has a much shorter half-life than other β-blockersand is administered intravenously to treat hypertension and **acute supraventricular tachycardia when these occur during surgery.**
- Esmolol is rapidly metabolized to inactive compounds by plasma esterase enzymes.

- **Metoprolol** is used to treat **hypertension, angina pectoris, and acute myocardial infarction. It** can be administered orally or parenterally, and it is extensively metabolized by cytochrome P450 enzymes before undergoing renal excretion.

α & β- Adrenoceptor Antagonists

- **Carvedilol and labetalol are agents that block both α- and β-adrenoceptors.**
- Carvedilol blocks β_1-, β_2-, and α1-adrenoceptors, and possesses antioxidant activity.
- Each of these actions contributes to its cardioprotective effects in persons with myocardial infarction.
- The antioxidant effects of carvedilol include

  (1) inhibition of lipid peroxidation in myocardial membranes, (2) scavenging of free radicals, and (3) inhibition of neutrophil release of O2.

α & β- Adrenoceptor Antagonists

- In addition, carvedilol has antiapoptotic properties that can prevent myocyte death and reduce infarct size in persons suffering from myocardial ischemia.
- For these reasons, carvedilol has been called a "third-generation β-blocker and neurohumoral antagonist," and its value in treating myocardial infarction has been established in clinical trials.

- Carvedilol decreases blood pressure and has been used in the treatment of hypertension. It also decreases cardiac afterload, increases cardiac output, and reduces mortality in patients with heart failure

α & β- Adrenoceptor Antagonists

- Labetalol is a nonselective β-blocker and a selective α1-blocker that is primarily used in the treatment of hypertension.
- It is 5 to 10 times more potent as a β-blocker than as an α-blocker, but both actions are believed to contribute to its antihypertensive effect.
- Labetalol decreases heart rate and cardiac output as a result of β_1-adrenoceptor blockade,
- and it decreases peripheral vascular resistance as a result of α_1-adrenoceptor blockade.

Therapeutic Uses

- Hypertension
- Angina prophylaxis
- Cardiac arrhythmias such as atrial fibrillation, atrial flutter and SVT
- Congestive cardiac failure such as carvedilol, metoprolol to reduce the mortality rate in CCF
- Pheochromocytoma
- Glacucoma
- Migraine prophylaxis

Therapeutic Uses

- Hyperthyroidism
- Essential tremors
- Acute anxiety states
- Alcohol withdrawal
- Dissecting aortic aneurysm

Therapeutic effects

- β-Blockers protect the heart from the oxygen-wasting effect of sympathetic inotropism by blocking cardiac β-receptors; thus, cardiac work can no longer be augmented above basal levels. This effect is utilized *prophylactically in angina pectoris to prevent* myocardial stress that could trigger an ischemic attack
- β-Blockers also serve to *lower cardiac rate (sinus tachycardia)* and *protect the failing heart against excessive* sympathetic drive
- β-Blockers lower *elevated blood pressure.*
- Applied topically to the eye, β-blockers are used in the management of *glaucoma; they lower production of aqueous* humor

Clinical Toxicity of the Beta-Blockers

- Minor toxic effects, Rash, fever, and drug allergy are rare.
- CNS effects include sedation, sleep disturbances, and depression. rarely, psychotic reactions
- Beta-receptor antagonist drugs with low lipid solubility are associated with a lower incidence of central nervous system adverse effects than compounds with higher lipid solubility

- The major adverse effects relate to the predictable consequences of β-blockade. β_2-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction without having these consequences in normal individuals.

Clinical Toxicity of the Beta-Blockers

- β_2-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction without affecting normal individuals.
- β_1-selective drugs may have less effect on airways than nonselective antagonists, they mustbe used very cautiously, if at all, in patients with reactive airways.

Clinical Toxicity of the Beta-Blockers

- β-blockade depresses myocardial contractility and excitability. In patients with abnormal myocardial function, cardiac output may be dependent on sympathetic drive.
- If this stimulus is removed by blockade, cardiac decompensation may ensue. Thus, caution must be

  exercised in using β -receptor antagonists in patients with compensated heart failure even though long-term use of these drugs in these patients may prolong life.

Clinical Toxicity of the Beta-Blockers

- A life-threatening adverse cardiac effect of a antagonist may be overcome directly with isoproterenol or with glucagon, which stimulates the heart via glucagon receptors, which are not blocked by antagonists)
- β-blockers may interact with the calcium

  antagonist verapamil; severe hypotension, bradycardia, heart failure, and cardiac conduction abnormalities have all been described. These adverse effects may even arise in susceptible patients taking a topical (ophthalmic) -blocker and oral verapamil.

Clinical Toxicity of the Beta-Blockers

- Evidence suggests that patients with ischemic heart disease may be at increased risk if blockade is suddenly interrupted.
- The mechanism of this effect is uncertain but might involve up-regulation of the number of β-receptors.
- The incidence of hypoglycemic episodes in diabetics that are exacerbated by β-blockers, so it is inadvisable to use antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions

Undesired effects

- ***Congestive heart failure***. *For a long time, β*-blockers were considered generally contraindicated in heart failure. Increased release of norepinephrine gives rise to an increase in heart rate and systolic muscle tension, enabling cardiac output to be maintained despite progressive cardiac disease.
- On the other hand, convincing clinical evidence demonstrates that, under appropriate conditions, low dosage β-blockers are able to improve prognosis in congestive heart failure. Protection against heart rate increases and arrhythmias may be important underlying factors.

SUMMARY OF IMPORTANT POINTS

- The α-adrenoceptor antagonists relax smooth muscle and decrease vascular resistance, whereas the β-adrenoceptor antagonists reduce heart rate and cardiac output. Both α- and β-blockers reduce blood pressure.
- The nonselective α-blockers include phenoxybenzamine (a noncompetitive blocker) and phentolamine (a competitive blocker).
- These drugs block both α1- and α2-adrenoceptors and are primarily used to treat hypertensive episodes caused by pheochromocytoma.

SUMMARY OF IMPORTANT POINTS

- The selective α1-blockers include alfuzosin, doxazosin, prazosin, tamsulosin, and terazosin. These drugs are used to treat chronic essential (primary) hypertension or to treat urinary obstruction caused by benign prostatic hyperplasia and other conditions.
- The nonselective β-blockers, which antagonize both β1- and β2- adrenoceptors, include nadolol, pindolol, propranolol, and timolol.
- In comparison with other β-blockers, pindolol has a higher degree of intrinsic sympathomimetic activity (partial agonist activity), and propranolol has a higher degree of membrane-stabilizing activity (local anesthetic activity).

SUMMARY OF IMPORTANT POINTS

- The selective β1-blockers include acebutolol, atenolol, esmolol, and metoprolol.
- These drugs cause less bronchoconstriction than do nonselective β-blockers.
- The β-blockers have a variety of clinical applications, including the prevention of migraine headache and the treatment of hypertension, angina pectoris, cardiac arrhythmias, and glaucoma.
- Carvedilol blocks α- and β-adrenoceptors and exerts other cardioprotective effects that make it useful in the treatment of myocardial infarction and heart failure.

- Thank you