Appendix B: Pharmacology

Autonomic Pharmacology

Pharmacology of the parasympathetic nervous system

Anticholinesterase drugs that slow the breakdown of acetylcholine will cause the wide spread stimulation of the autonomic ganglia, unless applied topically, and thus have limited therapeutic use. Organophosphorous nerve agents (WMDs) and some insecticides act by blocking the breakdown of acetylcholine. Cholinergic drugs that stimulate the nicotinic-n (N-n) receptors of the autonomic ganglia cause widespread stimulation and are of limited therapeutic use. Nicotine of course stimulates nicotinic-n (N-n) receptors. Drugs that block the stimulation of the nicotinic-n (N-n) receptors of the autonomic ganglia cause widespread suppression of the autonomic ganglia and also are of limited therapeutic use.

In contrast, muscarinic agonists that stimulate the muscarinic (M-1/M-3) receptors directly have more specific effects. Muscarinic agonists are often used for treatment of urinary retention, impaired gastrointestinal motility, glaucoma, and dry mouth. Muscarinic antagonists that block the muscarinic (M-1/M-3) receptors are common in therapeutics. Muscarinic antagonists are often used in trauma and surgical situations for blunting vagal tone, reducing secretions, increasing heart rate, and decreasing AV-block; in asthma to cause bronchial dilation; in ophthalmic exams to induce pupil dilation and relaxation of ciliary muscle; in prevention of nausea and vomiting; and in the treatment of overactive bladder. Table B.1 summarizes some of the common parasympathetic cholinergic drugs.

Pharmacology of the sympathetic nervous system

The limited utility of cholinergic drugs acting on the nicotinic-n (N-n) receptors of the autonomic ganglia was discussed in the previous section. The diversity of adrenergic receptors on the target tissues allows for a large variety of therapeutically useful drugs. The catecholamines are used variously to treat shock, acute asthma, cardiac arrest, and low blood pressure. Alpha adrenergic agonists are used to treat low blood pressure, vascular failure, and nasal congestion. Alpha-1 adrenergic antagonists are used to treat high blood pressure, and benign prostatic hyperplasia. Beta-2 adrenergic agonists are used to treat bronchospasm and asthma. Beta-1 adrenergic agonists are used in the treatment of cardiac decompensation. Beta-1 adrenergic antagonists are used in the treatment of high blood pressure, tachycardia, myocardial infarction, and congestive heart failure. Tables B.2 and B.3 summarize some of the common sympathetic adrenergic drugs.

Table B.1. Parasympathetic cholinergic drugs

Class	Generic Name	Brand Name	Action/Indication
Acetylcholinesterase	Physostigmine	Esserine (topical)	slows breakdown of Acetylcholine treatment of glaucoma
Nicotinic Agonist	Nicotine	Nicotrol (inhalation)	stimulates N-n receptors Aid to smoking cessation
Nicotinic Antagonist	Mecamylamine	Inversine	blocks N-n receptors management of severe hypertension
Muscarinic Agonists	Bethanechol	Urecholine	stimulates M-1/M-3 receptors treatment of urinary retention and impaired gastrointestinal motility
	Pilocarpine	Pilocar, Salagen	stimulates M-1/M-3 receptors treatment of glaucoma; dry mouth
Muscarinic Antagonists	Atropine	Atropine (injection)	blocks M-1/M-3 receptors reduction of secretions, blunt elevated vagal tone, increase heart rate, decrease AV-block
	Atropine	AtroPen (injection)	blocks M-1/M-3 receptors treatment of organophosphorous nerve poisoning
	Ipratroprium	Atrovent (inhalation)	blocks M-1/M-3 receptors treatment of bronchospasm
	Scopolamine	Isopto Hyoscine	blocks M-1/M-3 receptors induce pupil dilation and relaxation of ciliary muscle
	Scopolamine	Transderm Scop	blocks M-1/M-3 receptors prevention of nausea and vomiting, motion sickness
	Homatropine	Isopto Homatropine	blocks M-1/M-3 receptors induce pupil dilation
	Tropicamide	Mydiacyl	blocks M-1/M-3 receptors induce pupil dilation and relaxation of ciliary muscle
	Oxybutynin	Ditropan XL; Oxytrol	blocks M-1/M-3 receptors treatment of overactive bladder

Table B.2. Sympathetic adrenergic drugs: Catecholamines and alpha acting

Class	Generic Name	Brand Name	Action/Indication
Catecholamine	Epinephrine	Adrenalin (injection)	stimulates all Alpha/Beta receptors treatment of anaphylactic shock, acute asthma, cardiac arrest and acute ventricular standstill; increases heart rate and contractility via Beta-1 induces vasoconstriction via Alpha-1 and vasodilation via Beta-2 increases blood glucose
	Epinephrine	Adrenalin (inhalation)	stimulates all Alpha/Beta receptors treatment of bronchial asthma; induces bronchial dilation via Beta-2
	Norepinephrine	Levophed (injection)	stimulates all Alpha/Beta receptors treatment of acute hypotension; similar to epinephrine
	Dopamine	Dopamine (injection)	Dopamine/ Alpha/Beta treatment of shock and cardiac decompensation; induces vasodilation of renal vessels via D increases blood pressure and cardiac output via Alpha-1, Beta-1, Beta-2
Alpha Adrenergic Agonist	Amphetamine	Adderall	stimulates all Alpha/Beta receptors
	Ephedrine	Ephedrine (injection)	stimulates all Alpha/Beta receptors treatment of hypotension
	Phenylephrine	Neo-Synephrine (injection)	stimulates Alpha receptors treatment of low blood pressure; vascular failure; paroxysmal supraventricular tachycardia
	Phenylephrine	Vicks Nasex (nasal)	stimulates Alpha receptors treatment of nasal congestion via vasoconstriction
Alpha Adrenergic Antagonist	Phentolamine	Phentolamine	blocks Alpha-1 receptors treatment of high blood pressure
	Prazosin	Minipress	blocks Alpha-1 receptors treatment of high blood pressure
	Terazosin	Hytin	blocks Alpha-1 receptors treatment of benign prostatic hyperplasia and high blood pressure
	Doxazosin	Cardura	blocks Alpha-1 receptors treatment of benign prostatic hyperplasia and high blood pressure

Table B.3. Sympathetic adrenergic drugs: Beta acting

Class	Generic Name	Brand Name	Action/Indication
Beta Adrenergic Agonist	Terbutaline	Brethine (injection)	stimulates Beta-2 receptors treatment of bronchospasm
	Albuterol	Proventil (inhalation)	stimulates Beta-2 receptors treatment of bronchospasm
	Albuterol	Ventolin	stimulates Beta-2 receptors treatment of bronchospasm
	Salmeterol	Serevent (inhalation)	stimulates Beta-2 receptors treatment of asthma and prevention of bronchospasm
	Ritodrine	Yutopar	stimulates Beta-2 receptors treatment of premature uterine smooth muscle contraction
	Dobutamine	Dobutamine	stimulates Beta-1 receptors; treatment of cardiac decompensation
Beta Adrenergic Antagonist	Propranolol	Inderal	blocks Beta-1/Beta-2 receptors; treatment of hypertension, angina pectoris, supraventricular arrhythmias, ventricular tachycardia, myocardial infarction, essential tremor
	Metoprolol	Lopressor	blocks Beta-1 receptors; treatment of hypertension, angina pectoris, myocardial infarction
	Atenolol	Tenormin	blocks Beta-1 receptors; treatment of hypertension, angina pectoris, myocardial infarction
	Esmolol	Brevibloc	blocks Beta-1 receptors; treatment of supraventricular tachycardia or hypertension related to surgery
Alpha/Beta Adrenergic Antagonists	Labetalol	Trandate	blocks Alpha-1/Beta receptors; treatment of hypertension
	Carvedilol	Coreg	blocks Alpha-1/Beta receptors treatment of congestive heart failure, left ventricular dysfunction following myocardial infarction, hypertension

Cardiac Pharmacology

Many of the drugs with clinically important actions on the heart act on cholinergic receptors, adrenergic receptors, calcium channels, the production of nitric oxide, or the Na^+ / K^+ pumps. Most of the cholinergic and adrenergic drugs have already been seen above in the context of the autonomic nervous system.

Cholinergic drugs

- Atropine (Atropine) (injection) blocks the action of acetylcholine on all cholinergic muscarinic receptors.
    - Increases heart rate via blocking of M-2 receptors
    - Used in the treatment of bradycardia and AV-block.

Adrenergic drugs

- Epinephrine (Adrenalin) (injection) stimulates all adrenergic alpha and beta receptors and in the heart stimulates pacemaker cells and cardiac muscle largely via β-1.
    - Increases heart rate and contractility
    - Used in the treatment of acute asthma, anaphylactic shock, cardiac arrest and ventricular standstill.

- Dopamine (Dopamine) (injection) stimulates all adrenergic alpha and beta receptors and in the heart stimulates pacemaker cells and cardiac muscle largely via β-1.
    - Increases heart rate and contractility
    - Used in the treatment of shock and cardiac decompensation.

- Dobutamine (Dobutamine) (injection) stimulates adrenergic Beta receptors and in the heart stimulates pacemaker cells and cardiac muscle largely via β-1.
    - Increases heart rate and contractility
    - Used in the treatment of cardiac decompensation.

- Propranolol (Inderal®) blocks adrenergic Beta-1 and Beta-2 receptors and in the heart blocks pacemaker cells and cardiac muscle largely via β-1.
    - Decreases heart rate and contractility
    - Used in the treatment of hypertension, angina pectoris, supraventricular arrhythmias, ventricular tachycardia, myocardial infarction.

- Metoprolol (Lopressor®) and atenolol (Tenormin®) block adrenergic Beta-1 and Beta-2 receptors and in the heart blocks pacemaker cells and cardiac muscle largely via β-1.

    - Decreases heart rate and contractility
    - Used in the treatment of hypertension, angina pectoris, myocardial infarction

- Carvediolol (Coreg®) blocks adrenergic Alpha-1 and Beta receptors in the heart blocks pacemaker cells and cardiac muscle largely via β-1.

    - Decreases heart rate and contractility
    - Used in the treatment of congestive heart failure, and left ventricular dysfunction following myocardial infarction

Calcium channel blockers

- Nifedipine (Procardia®), a dihydropyridine, acts on dihydropyridine receptors blocks calcium L channels and the influx of calcium into cardiac muscle and smooth muscle.

    - Dilates blood vessels; decreases cardiac contractility;
    - Used in the treatment of vasoplastic angina, effort associated angina, and hypertension

- Amlodipine (Norvasc®), a dihydropyridine, acts on dihydropyridine receptors blocks calcium L channels and the influx of calcium into smooth muscle and cardiac muscle.

    - Dilates blood vessels decreases cardiac contractility;
    - Used in the treatment of hypertension, effort associated angina, and vasoplastic angina

- Diltiazem (Cardizem®) a benzothiazeine, blocks calcium L channels and the influx of calcium into smooth muscle and cardiac muscle.

    - Decreases cardiac contractility
    - Used in the treatment of hypertension and effort associated angina

- Verapamil (Isoptin®, Calan®) a phenylalkylamine, blocks calcium L channels and the influx of calcium into cardiac muscle and smooth muscle

    - Decreases cardiac contractility and heart rate; dilates blood vessels
    - Used in the treatment of vasoplastic angina and effort associated angina, atrial flutter and/or fibrillation, paroxysmal supraventricular tachycardia and essential hypertension

It has recently been shown that heart failure is associated with hyper-phosphorylation of the ryanodine receptor calcium channel in the sarcoplasmic reticulum (SR). The channels stay open too long and drain the calcium from the SR. The result is decreased entry of calcium into the intracellular fluid during each contraction and the deterioration of ventricular function. No drugs that act directly and specifically on the ryanodine receptors are clinically available. However, adrenergic beta blockers reduce the phosphorylation of the ryanodine receptors, increase calcium, and restore ventricular function (at least partially).

Nitric oxide donors

- Nitroglycerin (Nitroglycerin), donates nitric oxide which activates guanylyl cyclase and the conversion of GMP to cyclic GMP. The cGMP decreases the influx of calcium into smooth muscle.
    - Dilates blood vessels and increases coronary blood flow
    - Used in the treatment of angina

Cardiac glycosides

- Digoxin (Lanoxin®) inhibits Na^+ / K^+ pumps which cause elevated intracellular Na, increased Na^+-Ca^{2+} exchange, and elevated intracellular calcium.
    - Increases force of cardiac contraction.
    - Used in the treatment of mild to moderate heart failure

Vascular Pharmacology

Many of the drugs with clinically important actions on the blood vessels act on cholinergic receptors, adrenergic receptors, angiotensin II receptors, calcium channels, or the production of nitric oxide. Most of the cholinergic and adrenergic drugs have already been seen in the context of the autonomic nervous system and the heart.

Cholinergic nicotinic antagonists

- Mecamylamine (Inversine) (injection) block cholinergic N_n receptors in parasympathetic and sympathetic gangla.
    - Decreases autonomic transmission
    - Used in the treatment of severe hypertension.

Adrenergic agonists and antagonists

- Epinephrine (Adrenalin) (injection) stimulates all adrenergic alpha and beta receptors.
    - Increases vasoconstriction via α-1 receptors; increases vasodilation via β-2 receptors
    - Used in the treatment of acute asthma, anaphylactic shock, cardiac arrest and ventricular standstill.
- Norpinephrine (Levophed®) (injection).
    - Increases heart rate and contractility via β-1 receptors
    - Used in the treatment of acute hypotension.
- Dopamine (Dopamine) (injection) stimulates all adrenergic alpha and beta receptors.
    - Increases vasoconstriction via α-1 receptors; increases vasodilation in kidney via D receptors
    - Used in the treatment of shock and cardiac decompensation.
- Ephedrine (Ephedrine) (injection) and phenylephrine (Neo-Synephrine®) (injection) stimulates all adrenergic alpha and beta receptors.
    - Increases vasoconstriction via α-1 receptors
    - Used in the treatment of hypotension and vascular failure.

- Phentolamine (Phentolamine) and prazosin (Minipress®) blocks alpha-1 receptors.
    - Decreases vasoconstriction via blocking α-1 receptors
    - Used in the treatment of high blood pressure.
- Terazosin (Hytin®) and Doxazosin (Cardura®) blocks alpha-1 receptors.
    - Decreases vasoconstriction via blocking α-1 receptors
    - Used in the treatment of benign prosatic hyperplasia and high blood pressure.
- Labetalol (Trandate®) and Carvediolol (Coreg®) blocks adrenergic Alpha-1 and Beta receptors.
    - Decreases vasoconstriction via blocking α-1 receptors
    - Used in the treatment of hypertension; congestive heart failure, and left ventricular dysfunction following myocardial infarction

Angiotensin converting enzyme inhibitors and angiotensin antagonists

- Lisinopril (Prinivil®, Zestril®) and Captopril (Capoten®), inhibit angiotensin converting enzyme and thus reduce the production of angiotensin II.
    - Dilates blood vessels
    - Used in the treatment of high blood pressure, and in the adjunctive therapy of heart failure and following myocardial infarct.
- Losartan (Cozaar®) and Valsartin (Diovan®), block angiotensin AT-1 receptors and thus the action of angiotensin II on blood vessels, adrenal cortex, posterior pituitary, and kidney.
    - Dilates blood vessels, deceases secretion of aldosterone, decreases secretion of vasopressin, and decreases reabsorption of sodium by the kidney.
    - Used in the treatment of high blood pressure, hypertension in some patients with left ventricular hypertrophy, and in nephropathy in patients with type-2 diabetes; and in heart failure.

Calcium channel blockers

- Nifedipine (Procardia®), a dihydropyridine, acts on dihydropyridine receptors blocks calcium L channels and the influx of calcium into smooth muscle and cardiac muscle.
    - Dilates blood vessels; decreases cardiac contractility;
    - Used in the treatment of vasoplastic angina, effort associated angina, and hypertension

- Amlodipine (Norvasc®), a dihydropyridine, acts on dihydropyridine receptors blocks calcium L channels and the influx of calcium into smooth muscle and cardiac muscle.
    - Dilates blood vessels decreases cardiac contractility;
    - Used in the treatment of hypertension, effort associated angina, and vasoplastic angina
- Diltiazem (Cardizem®) a benzothiazeine, blocks calcium L channels and the influx of calcium into smooth muscle and cardiac muscle.
    - Decreases cardiac contractility
    - Used in the treatment of hypertension and effort associated angina
- Verapamil (Isoptin®, Calan®) a phenylalkylamine, blocks calcium L channels and the influx of calcium into cardiac muscle and smooth muscle
    - Decreases cardiac contractility and heart rate; dilates blood vessels
    - Used in the treatment of vasoplastic and effort associated angina, atrial flutter and/or fibrillation, paroxysmal supraventricular tachycardia and essential hypertension

Nitric oxide donors

- Nitroprusside (Nitropress®), donates nitric oxide which activates guanylyl cyclase and the conversion of GMP to cyclic GMP. The cGMP decreases the influx of calcium into smooth muscle.
    - Dilates blood vessels
    - Used in the treatment of hypertensive crisis and to produce controlled hypotension during surgery

Respiratory Pharmacology

Many of the drugs with clinically important actions on the lungs and bronchial tree act on cholinergic receptors, adrenergic receptors, or on inflammatory responses. Most of the cholinergic and adrenergic drugs have already been seen in chapter 13 in the context of the autonomic nervous system. In addition, some of the drugs listed below have been seen in chapter 16 and 17 to affect the heart and blood vessels.

Cholinergic muscarinic antagonists

- Ipratropium (Atrovent®), is an inhaled muscarinic antagonist.
    - Blocks cholinergic muscarinic M-3 receptors and decreases bronchoconstriction.
    - Often used to reduce bronchospasm, alone or in conjunction with beta adrenergic bronchodilators, in the treatment of COPD.

Adrenergic agonists

- Albuterol (Proventil®) and salmeterol (Serevent®) are inhaled beta-2 adrenergic agonists.
    - Increases bronchodilation via β-2 receptors
    - Used to prevent bronchospasm, and in the maintenance treatment of asthma..

Steroids

- Prednisone (Deltasone®) is a systemic steroid.
    - Used to reduce inflammation in the prophylactic treatment of asthma.
- Fluticasone (Flovent®), and Triamcinolone (Azmacort®) are inhaled steroids.
    - Used to reduce inflammation in the prophylactic treatment of asthma.

Leukotriene antagonists

- Montelukast (Singulair®) is a leukotriene receptor antagonist.

Used to reduce airway edema and smooth muscle contraction caused by inflammation in asthma

Renal Pharmacology

Diuretics

- Furosemide (Lasix®) inhibits Na^+, Cl^-, and K^+ reabsorption from the proximal and distal convoluted tubules and especially from the nephron loop ("loop diuretic").
    - Without the reabsorption of Na^+ and Cl^- the osmolarity of the peritubular interstitial fluid decreases, passive water reabsorption decreases and urine volume increases.
    - Furosemide is a potent diuretic.
- Hydrochlorothiazide (HCTZ) inhibits Na^+ and Cl^- reabsorption from the distal convoluted tubule with little effect on K^+. There is also stimulation of Ca^{2+}** reabsorption.
    - Without the reabsorption of Na^+ the osmolarity of the peritubular interstitial fluid decreases, passive water reabsorption decreases and urine volume increases. With increased reabsorption of Ca^{2+} urine Ca^{2+} concentration decreases and the likelihood of kidney stone formation decreases.
- Amiloride (Midamor®) inhibits Na^+ reabsorption from the distal convoluted tubule and collecting tubule and stimulates the reabsorption of K^+, H^+, and Mg^{2+} ("K^+ sparing diuretic").
    - Without the reabsorption of Na^+ the osmolarity of the peritubular interstitial fluid decreases, passive water reabsorption decreases and urine volume increases.
    - Amiloride is a weak diuretic compared to hydrochlorothiazide.

Vasopressin agonists and antagonists

- Vasopressin (Pitressin®) (injection) and desmopressin (DDAVP®) stimulates all vasopressin receptors, and in the kidney increases the number of water channels in the collecting tubule via V2 receptors and stimulates the reabsorption of water.
    - With more water channels, passive water reabsorption increases and urine volume decreases.
    - Used in the treatment of diabetes insipidus
- Conivaptin (Vaprisol®) (injection) blocks V1a and V2 vasopressin receptors and in the kidney decreases the number of water channels in the collecting tubule via block of V2 receptors and inhibits the reabsorption of water.
    - With fewer water channels, passive water reabsorption decreases and urine volume increases.
    - Used in the treatment of euvolemic hyponatremia in hospitalized patients

Adrenergic agonists

- Epinephrine (Adrenalin) (injection) stimulates all adrenergic alpha and beta receptors and in the kidney stimulates juxtaglomerular cells via β-1 receptors.

    - Increases production of renin via β-1 receptors, leading to increases in angiotensin
    - Used in the treatment of anaphylactic shock, cardiac arrest and ventricular standstill.

- Dobutamine (Dobutamine) (injection) stimulates adrenergic Beta receptors and in the kidney stimulates juxtaglomerular cells via β-1 receptors.

    - Increases production of renin via β-1 receptors, leading to increases in angiotensin
    - Used in the treatment of cardiac decompensation.

Angiotensin converting enzyme inhibitors and angiotensin antagonists

- Lisinopril (Prinivil®, Zestril®) and Captopril (Capoten®), inhibits angiotensin converting enzyme and thus reduce the production of angiotensin II and thus its action on blood vessels, adrenal cortex, posterior pituitary, and kidney.

    - Dilates blood vessels, decreases secretion of aldosterone, decreases secretion of vasopressin, and decreases reabsorption of sodium by the kidney.
    - Used in the treatment of high blood pressure, and in the adjunctive therapy of heart failure and following myocardial infarct.

- Losartan (Cozaar®) and Valsartin (Diovan®), block angiotensin AT-1 receptors and thus the action of angiotensin II on blood vessels, adrenal cortex, posterior pituitary, and kidney.

    - Dilates blood vessels, decreases secretion of aldosterone, decreases secretion of vasopressin, and decreases reabsorption of sodium by the kidney.
    - Used in the treatment of high blood pressure, hypertension in some patients with left ventricular hypertrophy, and in nephropathy in patients with type-2 diabetes; and in heart failure.