Sympathomimetic Drugs

Drug	Effect	Note
Direct-acting Sympathomimetic Drugs		
• **Norepinephrine (Noradrenaline)**	-β and α agonist -Constriction of the skin vessels & the splanchnic vessels -Increases peripheral resistance and both diastolic and systolic blood pressure. -Treatment of Acute Hypotension	-Acts equally on α1, α2, β1 receptors and much less on β2
• **Epinephrine (Adrenaline)**	-β and α agonist -Constriction of the skin vessels & the splanchnic vessels -Causes a rise in systolic BP by its positive inotropic and chronotropic actions on the heart (β1) and the vasoconstriction induced in many vascular beds (α). -Activates β2 receptors in skeletal muscle blood vessels, leading to their dilation. Total peripheral resistance may fall. -Activation of β2 → glycogenolysis in the liver - Activation of β3→ lipolysis → increases free fatty acids	-Acts on all alpha and beta receptors equally -Very potent vasoconstrictor and cardiac stimulant -Used in the temporary emergency management of complete heart block and cardiac arrest. -Applied topically for epistaxis or for gingivectomy -Favored agent for prolonging the duration of local anesthetics -Is used in anaphylaxis (Glucocorticoids and antihistamines may be useful as secondary therapy in anaphylaxis)
• **Phenylephrine**	-α agonist -Arterial and veno-constriction -Increases peripheral arterial resistance which leads to a rise in blood pressure (BP) -Decreases venous capacitance - Effective mydriatic and decongestant (used in nasal decongestant sprays) -Treatment of Acute Hypotension	-Selective α1 agonist, weak effect on α2 and nearly none on β receptors -None catecholamine, not inactivated by COMT & has a longer duration of action than the CA -Can be used in treatment of chronic orthostatic hypotension. -Used in the temporary emergency management of

Sympathomimetic Drugs

Drug	Effect	Note
• **Phenylephrine (Cont.)**		complete heart block and cardiac arrest.
• **Methoxamine**	-α agonist - a prolonged increase in BP due to vasoconstriction & a vagally mediated bradycardia -Treatment of Acute Hypotension	-Selective α1 agonist, weak effect on α2 and nearly none on β receptors -None catecholamine
• **Clonidine**	-α agonist -α 2 agonists are used in the treatment of hypertension -Stimulates α2 adrenoceptors in the vasomotor centre in brainstem causing a decrease in BP and cardiac output -High dose activates peripheral presynaptic autoreceptors on adrenergic nerve ending mediating negative feedback suppression of NE release -Overdose stimulates peripheral postsynaptic α1 adrenoceptors & cause hypertension by vasoconstriction. -Decreases heart rate (↓ NE release) and through a vagomimetic action. -Used in: ADHD, opioid withdrawal, restless legs syndrome, hypertension, alcohol withdrawal -Low dose of Clonidine is used in migraine prophylaxis, menopausal flushing and chorea	-Action on α2 is more than on α1, nearly none on β receptors -Has a sedative, analgesic, antishivering and diuretic actions -The site for the sedative action is in the locus ceruleus of the brain stem -The site for the analgesic action is in the spinal cord - Side effects: Sedation, dry mouth, dizziness and constipation
• **Guanfacine**	-A entrally acting α 2-selective agonist -Used in the treatment of hypertension	

Sympathomimetic Drugs

Drug	Effect	Note
• **Dexmedetomidine**	-A centrally acting α 2-selective agonist -Used for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.	-It reduces the requirements for opioids in pain control
• **Methylnorepinephrine**	-α agonist -α 2 agonists are used in the treatment of hypertension	-Action on α2 is more than on α1, nearly none on β receptors
• **Methyldopa**	-Metabolized to α-methyl norepinephrine, which then lowers arterial pressure by **activation** of presynaptic α2 receptors in the brainstem which reduce sympathetic outflow, lowering blood pressure (similar to clonidine) and a **reduction** reducing plasma renin activity.	-Used for treatment of hypertension during pregnancy as a replacement for ACE inhibitors & angiotensin II receptor blockers (which are more efficacious, but are strongly contraindicated in pregnancy)
• **Oxymetazoline**	-Direct-acting α1 agonist with significant affinity for α 2A receptors. -Used as a long topical decongestant because of promoting constriction of the nasal mucosa.	-When taken in large doses, oxymetazoline may cause hypotension, because of a central clonidine -like effect.
• **Apraclonidine**	-Alpha 2-selective agonist that also lower intraocular pressure, used in glaucoma.	
• **Dobutamine**	-β agonist -The resultant effects of dobutamine is β 1 stimulation. -Has a positive inotropic action caused by the isomer with predominantly β1 receptor activity. -Has relatively greater inotropic	-Selective β1 agonist, less effect on β2 and no effect on α receptors -Racemic mixture of (–) and (+) isomers. The (+) isomer is a potent β 1 agonist and an α 1 receptor antagonist. The (–) isomer is a potent α 1 agonist

Sympathomimetic Drugs

Drug	Effect	Note
• **Dobutamine (Cont.)**	than chronotropic effect compared with isoproterenol. -Short-term relief of heart failure	
• **Albuterol (Salbutamol), Terbutaline, Ritodrine**	- β agonist -Salbutamol & Terbutaline are used for treatment of bronchial asthma -Ritodrine & terbutaline are used to achieve uterine relaxation in premature labor	-Selective β2 agonist, less effect on β1 and no effect on α receptors -Metaproterenol is also used for the treatment of bronchial asthma
• **Isoproterenol**	-β agonist -Has positive chronotropic and inotropic actions (β1) & is a potent vasodilator (β 2). -Maintains or slightly increases systolic pressure -Lower diastolic pressure, so that mean blood pressure is decreased -Beta-receptor activation results in increased calcium influx in cardiac cells -Pacemaker activity is increased (positive chronotropic effect) -Conduction velocity in the AV node is increased (positive dromotropic effect), and the refractory period is decreased. -Intrinsic contractility is increased (positive inotropic effect).	-Affects β1 and β2 equally, no effect on α receptors -The direct effects on heart rate (HR) may be dominated by a reflex response to BP changes. -Physiologic stimulation of the heart by catecholamines increases coronary blood flow
• **Dopamine**	**-(Low infusion)** → vasodilation of renal, splanchnic, coronary, and cerebral vessels, via activation of D1 receptors -Activation of the D1 receptors in the renal vasculature induce natriuresis (↑Na+ excretion).	-The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output) -At low doses, peripheral resistance may decrease

Sympathomimetic Drugs

Drug	Effect	Note
Dopamine (Cont.)	**-(Moderate infusion)** → stimulates β1 receptors in the heart leading to increasing contractility & the HR increases slightely. -Used to treat congestive heart failure **-(High infusion)** → activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed (α receptor). -short-term relief of heart failure	-High rates of infusion of dopamine may mimic the actions of epinephrine - Endogenous DA regulates sodium excretion and renal function. Its deficiency in the basal ganglia leads to Parkinson's disease, which is treated with its precursor levodopa. Dopamine antagonists are antipsychotic drugs.
• **Miodrine**	-α1 agonist -Used in the treatment of orthostatic hypotension, due to impaired autonomic nervous system function -Although the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, it may cause hypertension when the subject is supine.	- A prodrug, enzymatically hydrolyzed to a selective α 1-receptor agonist
• **Ephedrine**	-It releases NE (indirect activation) & activates β2 receptors directly -It is a mild CNS stimulant -Bronchodilator, Decongestant and also used as a pressor agent during spinal anesthesia - Can be used in treatment of chronic orthostatic hypotension.	-The Plant Ephedra sinica has been used in traditional Chinese medicine for 5,000 years for the treatment of asthma, hay fever & the common cold -Has high bioavailability & a relatively long duration. -Useful in the treatment of stress incontinence
• **Pseudoephedrine**	-Useful in the treatment of stress incontinence	-One of four ephedrine enantiomers. -Available over the counter as a component of many decongestant mixtures

Sympathomimetic Drugs

Drug	Effect	Note
Indirect-acting Sympathomimetic Drugs		
• **Cocaine**	-Inhibits the reuptake of released NE by interfering with the action of the NE transporter -Major action in the CNS is to inhibit dopamine reuptake into neurons in the pleasure centers -Used for nasopharyngeal surgery because it combines a hemostatic effect with local anesthesia	-Readily enters CNS causing an amphetamine-like psychological effect that is shorter lasting and more intense than amphetamine -It can be smoked, snorted into the nose, or injected. It is a heavily abused drug.
• **Amphetamine**	-Increases the release of NE and dopamine -Actions vary from mild alerting, with improved attention to boring tasks to full-blown psychotic behavior -May also cause elevation of mood, insomnia, euphoria, & anorexia -Causes a depressant effect on appetite	-Non catecholamine, readily enters the CNS -Its D-isomer is more potent than the L-isomer.
• **Methamphetamine**	Very similar to amphetamine with an even higher ratio of central to peripheral action	
• **Methylphenidate**	-Its 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**	-A psychostimulant. -Inhibits both NE & DA transporters, & increases interstitial concentrations of NE, DA , serotonin and glutamate while decreasing GABA levels.	-Modafinil may also be useful in ADHD.

Sympathomimetic Drugs

Drug	Effect	Note
• **Modafinil (Cont.)**	-It is used primarily to improve wakefulness in narcolepsy. It is often associated with mild increases in BP & HR.	
• **Tyramine**	-Indirect sympathomimetic action caused by the release of stored catecholamines -In patients treated with MAO inhibitors, tyramine may cause marked increases in blood pressure (Cheese reaction).	-Found in ↑ conc. in some fermented foods such as cheese. -Metabolized by MAO in GIT & the liver so it is inactive orally
• **Sibutramine**	A serotonin and NE reuptake inhibitor and was used as appetite suppressant for long-term treatment of obesity.	
• **Atomoxetine**	A selective inhibitor of the NE reuptake transporter used in the treatment of attention deficit disorders	
Dopamine Agonists		
• **Levodopa**	Valuable in the treatment of Parkinson's disease	Converted to dopamine in the body
• **Fenoldopam**	-A D1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds. -The primary indication for fenoldopam is in the IV treatment of severe hypertension	

Agonists Effects on Adrenergic Receptors

α1	α2	β1	β2	β3
-Mediate contraction in (bladder base, urethral sphincter, prostate) and control urination -In the eye → Mydriasis -Nasal mucosa → local vasoconstriction causes decongestant action. -Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation-	- Mediate contraction in (bladder base, urethral sphincter, prostate) and control urination - α 2 agonists are used in the treatment of hypertension -Increases the outflow of aqueous humor from the eye → can be used clinically to reduce intraocular pressure (glaucoma)\ -In pancreatic islets → decreases insulin secretion -Inhibits renin secretion -Decrease BP through actions in the CNS even though direct application to a blood vessel may cause vasoconstriction	- In the heart → increases cardiac output -Stimulates renin secretion	-In bronchial smooth muscle leads to bronchodilation -Vasodilation in vascular beds of sk. Muscles (↑ blood flow during exercise) -In pancreatic islets → increases insulin secretion -Glycogenolysis in the liver, increasing glucose release into the blood -Promotes uptake of K into cells, leading to a fall in extracellular potassium	-Increase lipolysis with enhanced release of free fatty acids and glycerol into the blood

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
α-adrenoceptor Antagonists		
• **Phentolamine**	-A non-selective α blocker -Reduces peripheral resistance (α1) and causes cardiac stimulation (α 2 receptors blockade enhances release of NE) -Minor inhibitory effects at 5HT receptors -Agonist effects at muscarinic (salivary, sweat, lacrimal) and H1 and H2 receptors (increases acid secretion). -Uses: diagnostic of pheochromocytoma, control of hypertension due to clonidine withdrawal, cheese reaction. -Used to counteract vasoconstriction due to alpha agonists.	-Competitive α1 and α2 antagonist -Adverse effects: severe tachycardia, arrhythmias, and myocardial ischemia. - Used in treatment of overdose of α1 agonists
• **Prazosin**	- Highly selective α1 blocker & less potent at α 2 receptors - Relaxes both arterial and venous vascular sm muscle & smooth muscle in the prostate, due to blockade of α 1 receptors with no or little tachycardia - Favorable effect on plasma lipids: increase HDL/LDL ratio. -Uses: antihypertensive, benign prostatic hyperplasia (BPH), blocks α1 in bladder trigone & prostate & decreases tone & improves urine flow . -Used in peripheral vascular disease: Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation).	- Extensively metabolized, only 50% is available after oral administration. -The half-life is 3 hours. - Adverse effects: First dose phenomenon i.e. postural hypotension with initial doses.
• **Phenoxybenzamine** • **Phenoxybenzamine (Cont.)**	-A non-selective α blocker -Blocks α1 & to less extent α2 receptors. -Inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.	-Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h) - Absorbed poorly but usually given orally

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
	-causes little fall in BP in normal supine individuals, it reduces BP when sympathetic tone is high, e.g., as a result of upright posture. -Used in treatment of pheochromocytoma, peripheral vascular disease -Used in peripheral vascular disease: Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation).	-Adverse effects: orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.
• **Terazosin**	-Used in treatment of benign prostatic hyperplasia	High bioavailability. The half-life is 9–12 hours
• **Doxazosin**	-Used in treatment of benign prostatic hyperplasia	Has a longer half-life of about 22 hours
• **Tamsulosin**	-Uroselective α1A blocker. α 1A are predominant in bladder base & prostate - Used in treatment of benign prostatic hyperplasia -No effect on BP and heart rate	-30 times high affinity for α1A -High bioavailability and a half-life of 9–15 hours. Side Effects: Dizziness & retrograde ejaculation -Preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists
• **Yohimbine**	-α 2-selective antagonist. -Blocks other receptors also – 5HT, DA -Increases ADH release -Enhances sexual activity – aphrodisiac - Sometimes used in the treatment of orthostatic hypotension because it promotes NE release through blockade of presynaptic α 2 receptors.	- An indole alkaloid -Was widely used to improve male erectile dysfunction but has been superseded by phosphodiesterase-5 inhibitors like sildenafil (viagra).
• **Metyrosine**	-α -methyltyrosine, a competitive inhibitor of tyrosine hydroxylase. -Used in inoperable or metastatic pheochromocytoma.	- Can cause extrapyramidal effects due to reduced dopamine levels

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
β-adrenoceptor Antagonists		
• **Propranolol**	-No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear. -It has no partial agonist action at β receptors, strong local anesthetic effect -Has been used extensively in patients with thyroid storm (severe hyperthyroidism) to control supraventricular tachycardia that often precipitate heart failure -Reduces the frequency and intensity of migraine headache -The somatic manifestations of anxiety may respond dramatically to low doses of propranolol, particularly when taken prophylactically -May be used in symptomatic treatment of alcohol withdrawal in some patient	-Prototype of β -blocking drug -High lipid solubility -Has low and dose-dependent bioavailability (first pass metabolism) -First-pass effect varies among individuals - A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period
• **Nadolol**	Non-selective beta blocker	Has a very long duration of action
• **Timolol**	-Non-selective beta blocker -No local anesthetic activity, used topically to treat glaucoma	
• **Sotalol** • **Sotalol (Cont.)**	-Nonselective beta blocker - Exhibits Class III antiarrhythmic properties, due to potassium channel blockade -Treats both ventricular & supraventricular arrhythmias	
• **Metoprolol**	-β1 Selective Blocker	- High lipid solubility -Less likely to worsen asthma

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
	used to treat angina and hypertension & also used to treat or prevent myocardial Infarction (AMI) without bradycardia.	
• **Atenolol**	- β1 Selective Blocker - Most commonly used in Hypertension & angina	-Low lipid solubility -Longer duration action -One dose/day -Side effects related to CNS are less prominent, no effect on bronchus, carbohydrate metabolism, lipids
• **Nebivolol**	-The most highly selective β 1 blocker. -↑ endothelial NO release (vasodilating effect) -Antioxidant, ccan protect the vascular wall from free radicals that damage blood vessels and thereby contribute to the progression of cardiovascular disease. Activates cardiac β3-adrenergic receptors (protective mechanism against heart failure and myocardial ischemia)	
• **Bisoprolol**	- β1 Selective Blocker -Used to treat hypertension, coronary heart disease, arrhythmias.	- Low lipid solubility -Longer duration of action -One dose/day
• **Esmolol**	- Ultra-short–acting β 1-selective blocker -Useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis and myocardial ischemia in acutely ill patients.	- Contains an ester linkage; esterases in red blood cells rapidly metabolize it -Has a short half-life (about 10 minutes) -Given by continuous IV infusions -Esmolol may be safer in critically ill patients who require a β -adrenoceptor antagonist
β Blockers with partial β-agonist activity		
• **Pindolol**	- A non-selective beta- adrenoceptor/5-HT1A antagonist	

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
	-Accelerates the antidepressant effect of selective serotonin reuptake inhibitors.	
• **Celiprolol**	- β 1-selective antagonist with a partial β2 -agonist activity & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation	
• **Acebutolol**	- a β 1-selective antagonist	
Drugs that block both α and β Receptors		
• **Labetalol**	- α and β blocker -Used in Hypertensive Emergencies -Causes Hypotension with less tachycardia than occurs with α blockers -it is a partial agonist at beta2- receptors	
• **Carvedilol**	-A nonselective beta blocker/alpha-1 blocker, calcium channel blocker -More potent at β than at α1 receptors -Antioxidant property -Used in Hypertension, Angina, congestive heart failure	
Ganglion-Blocking Drugs		
• **Tetraethylammonium (TEA)**	-First ganglion blocker, very short duration of action	
• **Hexamethonium ("C6")**	-The first drug effective for hypertension	
• **Decamethonium**	-"C10" analog of hexamethonium, is a depolarizing neuromuscular blocker	
• **Mecamylamine** • **Mecamylamine (Cont.)**	-Enters the CNS causing Sedation, tremor, choreiform movements, and mental abnormalities. -Blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to reduce nicotine craving in patients attempting to quit smoking.	-A secondary amine, developed to improve absorption from the GIT because the quaternary amines were poorly absorbed after oral administration.

Adrenoceptor Antagonists & Ganglion- Blocking Drugs

Drug	Effect	Note
• **Trimethaphan**	-Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.	- A short-acting ganglion blocker, is inactive orally & is given by intravenous infusion.

Blocking of α-receptors	Blocking of β-receptors	Ganglion Blocking
✓ **Leads to:** -A decrease in peripheral vascular resistance and blood pressure and may cause orthostatic hypotension. -Miosis -Nasal stuffiness(congestion) -Increasing urination -Treatment of Chronic Hypertension	✓ **Leads to:** -Heart: ↓ Heart rate, ↓Stroke volume (the volume of blood ejected by one contraction), ↓ Cardiac output, ↓ AV conduction velocity, ↓ O2 consumption. - Blood vessels: ↓BP both diastolic and systolic after continuous treatment. -Effects on the Respiratory Tract : β2 blockade in lungs can produce bronchoconstriction and increase in airway resistance, particularly in patients with asthma (not noticed in normal people) -Reduce intraocular pressure in glaucoma by decreasing aqueous humor production. -β-receptor antagonists increase LDL (the bad cholesterol) and triglycerides, and decrease HDL (the good cholesterol) by inhibiting lipolysis. Long term treatment of β-blockers might expose the patient to type 2 diabetes. -Glycogenolysis in the liver is inhibited after β2-receptor blockade. -Treatment of hyperthyroidism, β antagonists are beneficial in this condition due to blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine -β antagonists reduce certain tremors	✓ **Leads to:** -Sedation, tremor, choreiform movements, and mental abnormalities. -Eye: cycloplegia with loss of accommodation & moderate dilation of the pupil because parasympathetic tone usually dominates this tissue - Marked decrease in arteriolar and venomotor tone. -BP may fall because both peripheral vascular resistance and venous return are decreased -Orthostatic or postural hypotension, diminished contractility and a moderate tachycardia - Secretion & Motility are profoundly inhibited, and constipation can be marked - may precipitate urinary retention in men with prostatic hyperplasia -Sexual function is impaired in that both erection and ejaculation -Sweating is reduced by the ganglion-blocking drugs

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