PHARMACOLOGY

Lecture: Adrenergic drugs

OBJECTIVES:

- Identify the classification of adrenergic agonists
- Describe pharmacokinetics and dynamics of adrenergic agonists
- Differentiate between the actions of a and b-adrenoceptors agonists
- List the clinical uses of adrenergic agonists.
- know adverse effects & contraindications of adrenergic agonists
- Identify one specific adrenergic agonist for each of the following special uses: Hypotensive states, shock, heart failure, heart decompensation, asthma, premature labour…ect..

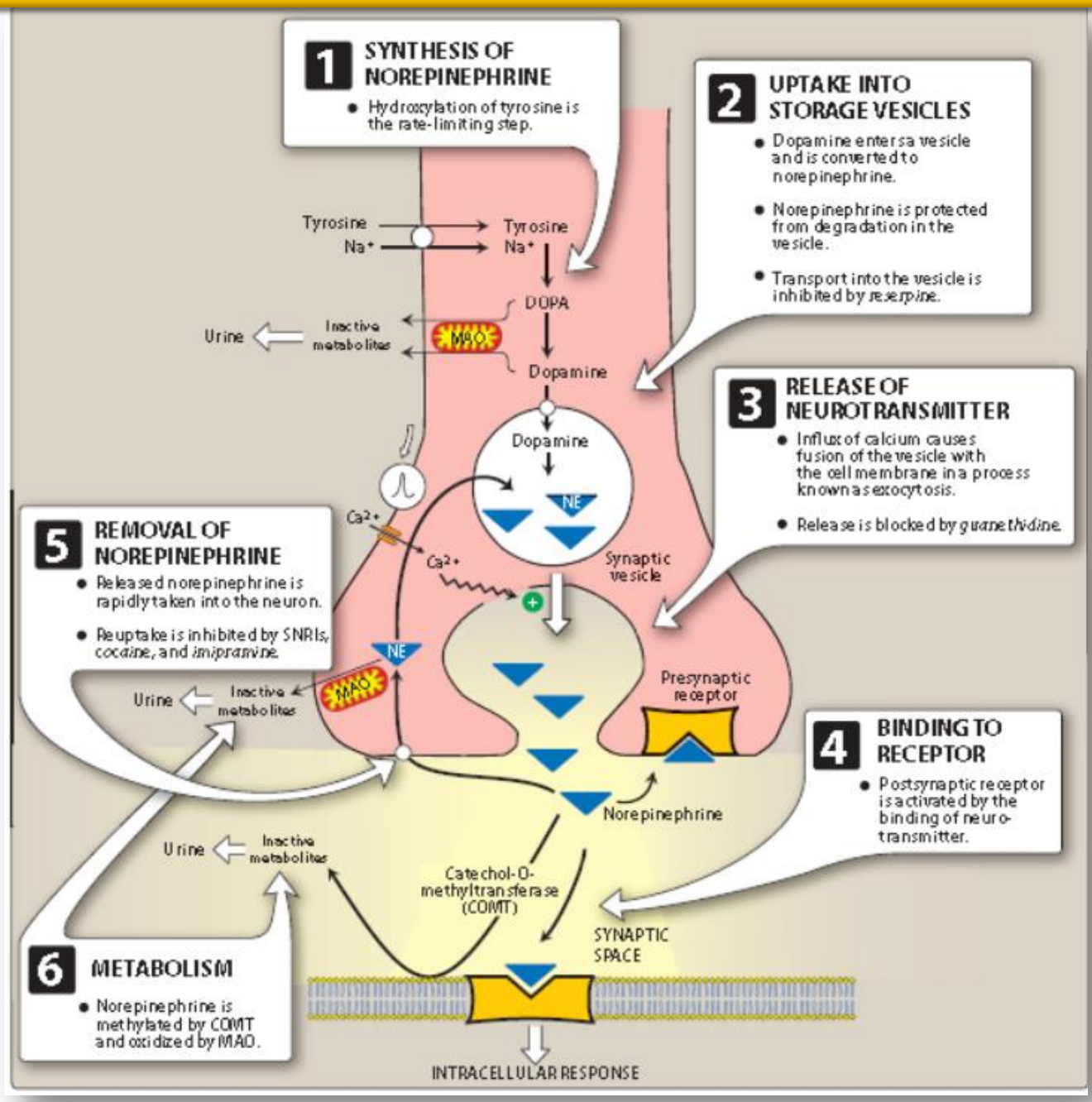
Terminology:

Chronotropic = increase cardiac output
Inotropic = increase cardiac force of contraction
Dromotropic = increase conduction velocity
Tocolytics (anti-contraction) are medications used to suppress premature labor.
Extravasation: leakage of drug from the vessel into tissues surrounding the injection site
Adrenaline = epinephrine (E)
Noradrenaline (NA) = norepinephrine (NE)

PHARMACOLOGY 435

- Important.
- Extra notes.

Neurotransmission at adrenergic neurons



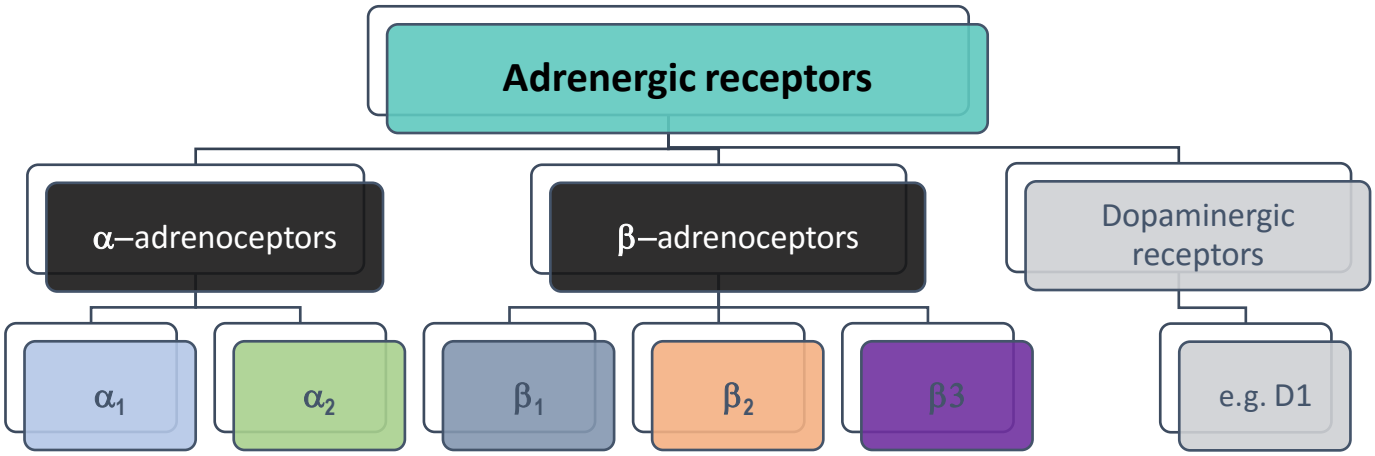
Adrenergic transmission:

1) Synthesis of norepinephrine
2) Storage of norepinephrine in vesicles
3) Release of norepinephrine
4) Binding to post synaptic receptors
5) Ending the action of NE by:

- Neuronal reuptake into neuron
- Monoamine oxidase (MAO) in neuronal mitochondria
- Catechol -O-methyl transferase (COMT) in synaptic space

Note: Adrenergic neurons release norepinephrine as the primary neurotransmitter.

Adrenergic receptors



α1	β2	β1	β3
Post-synaptic			
excitatory in function (cause contraction) except in GIT.	inhibitory in function (cause relaxation)	excitatory in function, present mainly in heart	In adipose tissue
Present mainly in smooth muscles.			
Contraction of pregnant uterus.	Relaxation of the uterus (Delay premature labor)	↑ heart rate: + chronotropic effect, Tachycardia ↑ force of contraction : + inotropic effect ↑ conduction velocity: + dromotropic effect ↑ blood pressure ↑ renin release Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.	↑ lipolysis ↑ free fatty acids.
Vasoconstriction of skin & peripheral blood vessels →increased peripheral resistance → hypertension.	Relaxation of skeletal & coronary blood vessels (vasodilatation)		
Relaxation of GIT muscles & urinary bladder's muscles. Contraction of GIT sphincter (constipation) & urinary bladder's sphincter (urinary retention).			
Contraction of radial muscle of eye causes active mydriasis	• Relaxation of bronchial smooth muscles • Tremor of skeletal muscles • ↑ lipolysis		
Increase blood glucose level (hyperglycemia) , by:			
• ↓insulin • ↑ glycogenolysis	•↑ glucagon release from pancreas •↑ liver & muscle glycogenolysis		

α2	β2
Pre-synaptic	
Inhibition of norepinephrine release (negative feed back mechanism).	Increase release of NE (Positive feed back mechanism).

Adrenergic agonist:

Adrenergic agonist "sympathomimetics" :

Drugs that produce an effect similar to that obtained by stimulation of the sympathetic nervous system.

Sympathetic actions:

- ✓ Mydriasis (dilatation of eye pupil)
- ✓ Increase heart rate.
- ✓ Bronchodilation
- ✓ Inhibit peristalsis of GIT and secretion.
- ✓ Relaxation of GIT muscles (constipation).
- ✓ Relaxation of urinary bladder.
- ✓ Relaxation of the uterus (Delay premature labor)
- ✓ Increase conversion of glycogen to glucose (hyperglycemia)

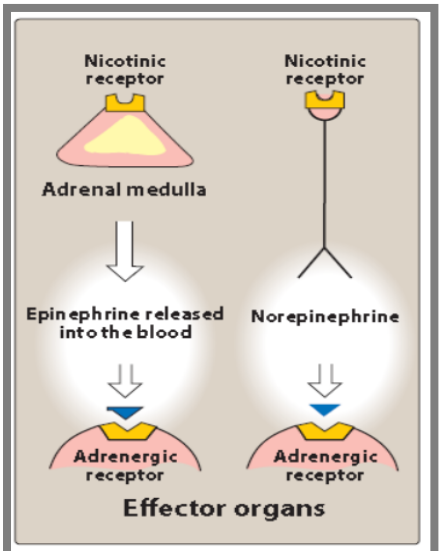


Figure 6.2
Sites of actions of adrenergic agonists.

Major effects mediated by α- and β-adrenoceptors:

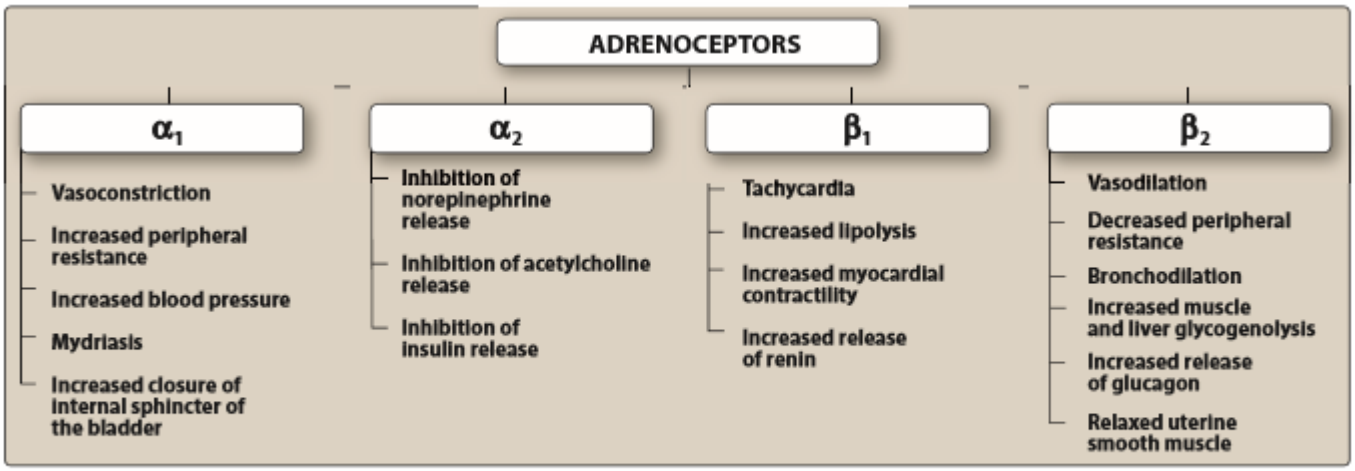


Figure 6.6
Major effects mediated by α- and β-adrenoceptors.

Classification of Adrenergic agonist:

They are classified according to:

1. Chemistry:

Catecholamines	Non-Catecholamines
Rapidly acting Have short half-life, due to rapid degradation by **MAO** & COMT	Delayed action Have Long half-life, because they resist degradation by MOA &COMT in GIT
Have catechol ring water soluble (polar) ,thus not effective orally and have Poor penetration to CNS	Lack catechol ring Lipid soluble , thus Effective orally and Cross BBB well , have Prominent CNS effects
Parenterally administered	Orally administered
e.g. **Natural**: NE, E, Dopamine **Synthetic**: Isoprenaline, dobutamine	e.g. Ephedrine, amphetamine, phenylephrine, methoxamine, salbutamol, ritoderine

2. Mode of action:

Direct

- Stimulate adrenergic receptors **directly**
  e.g. adrenaline, noradrenaline, dopamine, isoprenaline, phenylephrine, clonidine, dobutamine, salbutamol, methoxamine, naphazoline

Indirect

- **Stimulate adrenergic receptors by:**
- ↑ NE release from presynaptic adrenergic nerve endings.
  e.g. amphetamine
- Inhibit uptake of NE → ↑its availability in synapse.
  e.g. Cocaine & antidepressants

Dual

- Direct and indirect stimulation of adrenergic receptors (mixed)
- e.g. ephedrine, pseudoephedrine

3. Spectrum of action:

Non-Selective

- Norepinephrine (α_1; α_2; B_1)
- Epinephrine (α_1; α_2;β_1 ; β_2; $\beta3$)
- Dopamine (**D1**; α_1; B_1)
- Isoprenaline (B_1 ; β_2; $\beta3$)
- Ephedrine (α ; β)

Selective

- α_1; Phenylephrine
- α_2; Clonidine, Brimonidine
- β_1; Dobutamine
- β_2; Salbutamol, Terbutaline, Ritoderine

Direct acting adrenergic agonists

ADRENALINE

Receptor		Non-selective α_1; α_2; (predominate at high doses) B_1 ; β_2; $\beta 3$ (At low doses)
Overview		Natural catecholamine. It has fast onset & Short duration of action.
Admin.		Given I.V, S.C, inhalation, topically. Not effective orally (inactivated by intestinal enzymes), since it's a catecholamine
Action	**Heart**	inotropic, chronotropic, dromotropic (↑excitability) (β_1)
	Blood pressure	• ↑ systolic (β_1) / ↓ diastolic • high dose stimulates $\alpha 1$ → Hypertension • low dose stimulates $\beta 2$ → Hypotension
	Vascular SMC	constrict skin + peripheral (α_1) dilate coronary + skeletal (β_2)
	Non vascular SMC;	• Lung → bronchiodilatation (β_2) • GIT → ↓motility (β_2) / contract sphincter (α_1) • Bladder → ↓ detrusor "smooth muscle found in the wall of the bladder" (β_2) / contract trigone & sphincter (α_1) • Pregnant uterus → **tocolytic action** (anti-contraction) (β_2) • Eye → active mydriasis (α_1), no effect on accommodation
	Metabolism	↓insulin ($\alpha 1$) , ↑glucagon ($\beta 2$) ↑ liver glycogenolysis + sk. m. glycolysis ($\beta 2$) ↑ adipose lipolysis ($\beta 3$ /$\beta 2$)
	CNS	little, headache, tremors & restlessness (CNS effects 're not very prominent)
Indication	**locally:**	- as haemostatic (control bleeding) (α_1): Nasal pack in epistaxis and in dental practice - combined with local anesthetics to ↓ absorption & side effects of local anesthetics + ↑duration of action + ↓ bleeding from incision
	Systemically:	• In acute asthma. Given S.C. or by inhalation in emergency to produce bronchodilatation ($\beta 2$) + ↓mucosal edema (due to vasoconstriction by α_1) . Note: ***Selective β_2 are better*** • Drug of choice in Anaphylactic shock (Hypersensitivity reactions), given S.C. it is the physiological antagonist of histamine. Effects: ↑ BP & bronchodilation. • Cardiac arrest (I.V). to restore cardiac rhythm in patients with cardiac arrest.
ADRs		**-Tachycardia**, palpitation, arrhythmias, angina pains. - Headache, weakness**, tremors, anxiety** and restlessness. - Hypertension → cerebral hemorrhage and **pulmonary edema**. - Coldness of extremities → tissue necrosis and gangrene if extravasation - Nasal stuffiness & rebound congestion if used as decongestant
Contraindications		- Congestive heart disease (CHD), hypertension, peripheral arterial disease. - Hyperthyroidism. Thyroxine causes CVS abnormalities, adrenaline will therefore make it worse. - Ischemic heart disease (angina), Arrhythmia & Myocardial infarction - Closed-angle glaucoma: ciliary relaxation (due to mydriasis)→ ↓ filtration angle → ↑ IOP

Direct acting adrenergic agonists

	NORADRENALINE	Isoprenaline
Overview	**A naturel catecholamine, non-selective agonist** Adrenergic neurons release norepinephrine as the primary neurotransmitter.	• Synthetic direct acting catecholamine • show no presynaptic uptake nor breakdown by MAO which lead to longer action.
Adminis-	only administered by I.V , may cause necrosis using IM or SC	• Used mainly in cardiac arrest (Parenteral). • Rarely in acute attack of asthma (inhalation).
Receptor	**mainly on α adrenoceptors (α1, α2, β1, weak action on β2).**	non-selective β agonist It Acts on β1, β2, β3
Pharmacological actions	• Severe vasoconstriction **(α1).** Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β2 receptors on blood vessels supplying skeletal muscles. The weak β2 activity of *norepinephrine* also explains why it is not useful in the treatment of asthma or anaphylaxis. • ↑ BP [systolic & diastolic]. this stimulates the baroreceptors, inducing a rise in vagal activity (parasympathatic system) ➔ reflex bradycardia • Increase force of contraction **β1** but decrease H.R. **(**CO not much changed**)**	β1 • + inotropic effect, • + chronotropic effect • increase cardiac output (CO). β2 • Vasodilatation of blood vessels of skeletal muscles and coronaries. • Bronchodilatation . • Relaxation of uterus. • Hyperglycemia β3 lipolysis
indications	**Topically:** as a local haemostatic with local anesthetic to reduce tachycardia & irritability, but as side effect, may produce necrosis & sloughing of the skin. **Systemically:** hypotensive states : - in spinal anesthesia (Hypotension (Spinal shock) – commonly occurs due to sympathetic nervous system blockade) - in septic shock (hypotension) if fluid replacement and inotropics fail	Uses: • Used mainly in cardiac arrest *(Parenteral).* • Rarely in acute attack of asthma for bronchodilation *(inhalation).* Contraindications: In hyperthyroidism & Congestive heart disease

Direct acting adrenergic agonists

	DOPAMINE	DOBUTAMINE	Phenylephrine
Overview	- Natural catecholamine & CNS transmitter. -Released from postganglionic adrenergic fibres	• Synthetic catecholamine • Metabolized by COMT, thus has a short duration	• Synthetic **non catecholamine** • has prolonged duration of action, since it's Not inactivated by COMT
Administration	Given parentally by infusion	IV	Orally
Receptor	$D_1 > \beta_1 > \alpha_1$ (in order)	Selective β_1–agonist.	selective α_1
Pharmacological actions	**D1: Low dose** • vasodilatation of mesenteric, coronary, renal blood vessels. Thus improves blood flow to viscera • diuresis (increase excretion of urine) *Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis.* • Decrease BP **β1: intermediate dose** • +ve inotropic • +ve chronotropic effects • Increase BP **α1: high dose** • Vasoconstriction • hypertension	• On heart: +ve Inotropic with little chronotropic effect. as it increases cardiac output, with little increase in heart rate • On BP: Hardly any effect; β1 & β2 counterbalance + no α1 • No vasodilatation of renal blood vessels. (No effect on dopaminergic receptors)	• Myadritic action (α_1) • ↑ increased both systolic & diastolic blood pressure (hypertension) due to vasoconstriction (α_1) • reflex Bradycardia due to ↑ BP **Adverse effects:** Hypertension. Thus, another drug is more preferable to produce hypertension that doesn't last for long. This drug is Midodrine. It peaks in 20 min, duration 30 min only.
indications	**- Drug of choice in treatment of shocks** (hypotension); septic, Hypovolemic (after fluid replacement), cardiogenic. It increases the BP by β1 receptor but **without causing renal impairment (D1)** -so it's preferred to be used in shocks, because it protects the kidney from renal failure which could be caused by vasoconstriction- - Can be given in acute heart failure (HF) **but Dobutamine is better.**	• Given parentally by infusion for short term management of Cardiac decompensation after cardiac surgery, in acute myocardial infarction (AMI) & heart failure [AHF]. • It does not increase oxygen demand which made it preferred.	- **systemically**: Vasopressor **agent** in hypotension & terminates atrial tachycardia by its reflex bradycardia action. -**Topically**: • **Haemostatic, with Local anesthesia**. • Mydriatic (in ophthalmic solutions to facilitate eye examination) • **Nasal decongestant** topically, nasal drops in allergic rhinitis, cold

Direct acting adrenergic agonists

	Clonidine	Brimonidine	Salbutamol	Terbutaline	Ritordine
Over-view	Synthetic Imidazoline	Imidazoline	Synthetic non catecholamines		
Administration	Orally or patch		Orally, inhalation or parentral		Orally or injection
Receptor	Presynaptic α_2 agonist Remember: this receptor inhibits NE release	**α_2 agonist**	**selective B_2 agonists**		
Pharma-cological action	• Acts centrally (α2) at nucleus tractus solitarius to decrease sympathetic outflow to heart & vessels. • Inhibit sympathetic vasomotor centers.	used in glaucoma as it reduces formation of **aqueous humor** and therefore decrease intra-ocular pressure (IOP)	Bronchodilator or for acute attacks of asthma & COPD. N.B. Salmeterol & Formoterol are longer acting	**Bronchodilator** & **Tocolytic** (delay premature labor)	**Tocolytic** (relaxation of uterus to treat premature labor)
Indica-tions	**Antihypertensive drug:** used in essential hypertension to lower BP.				

NOTE: Any selective drug given in high dose turns to be NON-SELCTIVE.

Nasal & Ocular decongestants:				
	Phenethylamines		Imidazoline	
Drug	**Phenylephrine**	**Pseudoephedrine**	**Nephazoline**	**Oxymetazoline**
Indications	**Used for treatment of nasal stuffiness**			
Side effects	**Can cause nasal rebound.**			

Other nasal decongestants that are mentioned earlier: adrenaline + phenylephrine

Indirect & dual acting adrenergic agonists

Indirect acting:

AMPHETAMINE

mechanism of action	It acts indirectly by releasing NE from presynaptic stores at adrenergic terminals. It depletes vesicles from stored NE and thus cause Tachyphylaxsis (reduction of response after repeated administration)
Administration & metabolism	Absorbed orally, because it is a Synthetic non-catecholamine. Not destroyed by MAO (longer duration) , excreted mostly unchanged (increased excretion by acidification of urine).
Selectivity	Acts on α & β similar to epinephrine but has **CNS stimulant effects**
CNS effects	mental alertness, wakefulness, concentration & self-confidence
ADRS	- depression & fatigue on continued use - euphoria (a feeling or state of intense excitement and happiness which is what cause its addiction & abuse in use) - lose appetite & decrease weight - increase energy expenditure
extra information	Not used therapeutically anymore, because it induces psychic & physical dependence & psychosis
Cocaine	is an Indirect Adrenergic stimulants that inhibits the uptake of norepinephrine so it increases its availability in synapse

Dual acting:

EPHEDRINE

Overview	Plant alkaloid, synthetic, non-catecholamine, dual (mixed) acting
Spectrum of Action	Non selective , Acts on α & β
Pharmacokinetics	Absorbed orally, not destroyed by MAO or COMT → prolonged action
Mechanism of action	• Directly: direct action on receptors → down regulation of receptors • Indirectly: Release NE from adrenergic nerve endings Lead to depletion of stores then tachyphylaxsis
Action	• facilitation of neuromuscular transmission & retention of urine • it has CNS stimulant effects (less than amphetamine)
ADRS	• Drugs of abuse by athletes and prohibited during games, thus No more therapeutically used • Bi folded effect: activation fallowed by dropping; Because it depletes vesicles of stored NE it cause tachyphylaxsis
Pseudoephedrine	Dual acting , acts on CNS & has less pressor effects compared to ephedrine. Used as nasal & ocular decongestant & in flu remedies

Mind map

Drugs on the Autonomic nervous system

Cholinergic drugs
Act on the PNS

Adrenergic drugs
Act on the **Sympathetic** Nervous System (SNS)

Adrenergic Depressants (Antagonist)

Types

Adrenergic stimulants (Sympathomimetic)

According to chemistry

Catecholamine
Have catechol ring (polar) **E.g.**
Natural: **Adrenaline, Noradrenaline, Dopamine**
Synthetic: **Isoprenaline, Dobutamine**

Non-catecholamine
Lack catechol ring (Lipid soluble)
E.g. Ephedrine, Amphetamine, Phenylephrine, Methoxamine, Salbutamol, Ritodrine.

According to spectrum of action

Non-selective
- **Adrenaline** ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$)
- **Noradrenaline** ($\alpha_1, \alpha_2, \beta_1$)
- **Dopamine** (D_1, α_1, β_1)
- **Isoprenaline** ($\beta_1, \beta_2, \beta_3$)
- **Amphetamine** (α & β)
- **Ephedrine** (α & β)

Selective
- **Phenylephrine** (α_1)
- **Clonidine – Brimonidine** (α_2)
- **Dobutamine** (β_1)
- **Salbutamol, Terbutaline, Ritoderine** (β_2)

According to action

Direct
Direct stimulation of adrenergic receptors.
E.g. Epinephrine, NE, Phenylephrine…

Indirect
↑ NA release from presynaptic adrenergic nerve ending.
E.g. Amphetamine
Or inhibit NA uptake.
E.g. Cocaine & antidepressants.

Dual
Direct & indirect stimulation of adrenergic receptors.
E.g. Ephedrine, pseudoephedrine.

Receptors
Adrenergic
$\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$,
Dopamine receptors

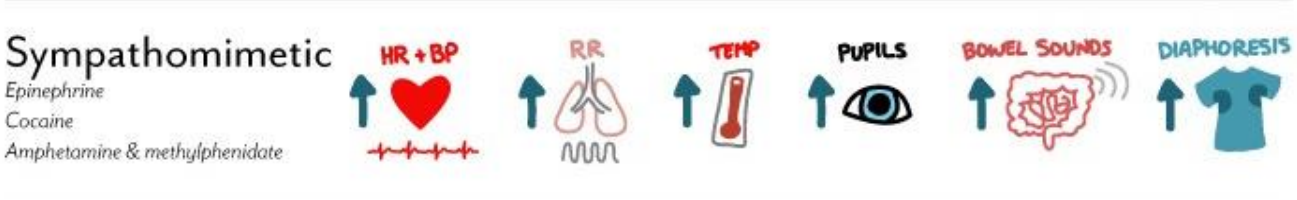
Organ	R.	Response
Eye:		
• Radial m.	α_1	• Contraction (mydriasis)
• Circular m.	---	
• Ciliary m.	β_2	• Relaxation
Lung:		
• Bronchial m.	β_2	• Relaxation.
Blood vessels:		
• Most (except Sk. m.)	α_1	• Contraction.
• Skeletal m.	β_2	• Relaxation.
GU:		
• Urinary sphincter.	α_1	• Contraction.
• Bladder wall.	β_2	• Relaxation (retention)
• Uterus, pregnant.	$\alpha_1;\beta_2$	• Contraction ; Relaxation.
• Uterus, nonpregnant.	β_2	• Relaxation.
• Penis, seminal vesicles.	α_1	• Ejaculation.
Kidneys	D_1	Vasodilatation and diuresis (increase excretion of urine).

Organ	R.	Response
Heart:		
• SA node	β_1	• ↑ HR. (**Chronotropic**)
• AV node	β_1	• ↑ velocity (**Dromotropic**)
• Contractility	β_1	• ↑ force (**Inotropic**)
GI:		
• Sphincter.	α_1	• Contraction (retention)
• Motility & tone.	α, β_2	• ↓
Secretory glands:		
• Sweat.	α_1	• Localized secretion.
• Intestinal.	α_2	• Inhibition.
• Bronchial.	--	
• Lacrimal.	α	• ↑ Secretion (moderate)
Metabolism:		
• Adrenal medulla.	N_N	• Secretion of catecholamines.
• Kidney.	β_1	• ↑ Renin release.
• Skeletal m.	β_2	• Glycogenolysis, ↑contractility.
• Pancreas.	α_2	• ↓ Insulin release.
• Fat cells.	β_3	• Lipolysis.

adrenergic drugs summary

Drug	Receptors	Function/Administration/ADRS/Contra.	Uses
Direct / Catecholamine / Non-selective			
Adrenaline	B ≥ α	**ADRS/Contra.:** • Tachycardia/CHD, Hypertension, angina. • Tissue necrosis/peripheral arterial disease. • Nasal stuffiness. Headache, tremors. • Closed-angle glaucoma. **Administration:** parenteral & by inhalation	• Status asthmatics (S.C./Inhalation) • Allergic reactions (S.C.) • Cardiac arrest (IV) • local hemostatic. • local anesthetics.
noradrenaline	$\alpha > \beta_1$	Sever vasoconstriction (α1), Reflex bradycardia, ↑ force of contraction but ↓ H.R. **Administration: Only IV**	• Hypertensive state • local hemostatic.
Isoprenaline	β > α	Long effect./ **Contra.:** Hyperthyroidism & CHD. **Administration:** inhalation	• Cardiac arrest (Parenteral) • Acute asthma (Inhalation)
Dopamine	$D_1 > \beta_1 > \alpha_1$	Has diuretic action /**Admin.:** parentally by infusion	Treatment of shock
Dobutamine	$\beta_1 > \beta_2 > \alpha_1$	**Administration:** IV	• Acute heart failure. • Cardiac decompensation.
Direct / Non-ctecholamine / Selective			
Midodrine & Phenylephrine	α_1	**Admin.:** Orally / **ADRS:** Hypertension. (Midodrine) peaks in 20min, duration 30min, it's better since it's short it doesn't cause severe tachycardia.	• **Hypotension**, tachycardia , • Local Hemostatic, with Local anesthesia. / Mydriasis. • Decongestant (*nasal & ocular)*
Clonidine	α_2	Synthetic, imidazoline. **Admin.:** Orally or as patch	Hypotension
Brimonidine	α_2	Is an imidazoline. **Admin.:** ocular route	Glaucoma
Salbutamol	β_2	**Admin.:** Orally, by inhalation or parenteral	Bronchodilator: Asthma and COPD
Terbutaline	β_2	**Admin.:** S.C	Bronchodilator, **Tocolytic**
Ritodrine	β_2	**Admin.:** Orally, or by injection.	**Tocolytic** for premature labor
Non-ctecholamine / Non-selective			
Indirect	**Amphetamine**	**ADRS:** Tachyphylaxis, euphoria, weight loss. **CNS:** mental alertness, wakefulness, concentration & self-confidence followed by depression & fatigue on continued use.	**Admin.:** Orally. Abused in sports. (Not used anymore)
Dual	**Ephedrine**	**ADRS:** Tachyphylaxis, urine retention	
Nasal & Ocular decongestant			
Direct	**Phenylephrine**	**Methoxamine**	**Nephazoline**	**Oxymetazoline**	**Otrivine**
Uses: treatment for nasal stuffiness / **ADRS:** Can cause nasal rebound.					
Dual	**Pseudoephedrine**				
CNS & pressor effects compared to ephedrine / works the same way as the "Nasal & Ocular Decongestants drugs" and for **flu**					

Drugs Summary



Agents specifically indicated for hypotension: Midodrine, Phenylephrine, Norepinephrine

Agents specifically indicated for cardiogenic shock (Acute Heart Failure):

Dobutamine, Dopamine, Epinephrine

Agents specifically indicated for shock: Dopamine, Norepinephrine

Agents specifically indicated for cardiac arrest: Dobutamine, Epinephrine, Norepinephrine

Agents specifically indicated for bronchial asthma:

Salbutamol, Salmeterol, Formoterol, Terbutaline, Isoprenaline

Agents specifically indicated for premature labour : Ritodrine, Terbutaline

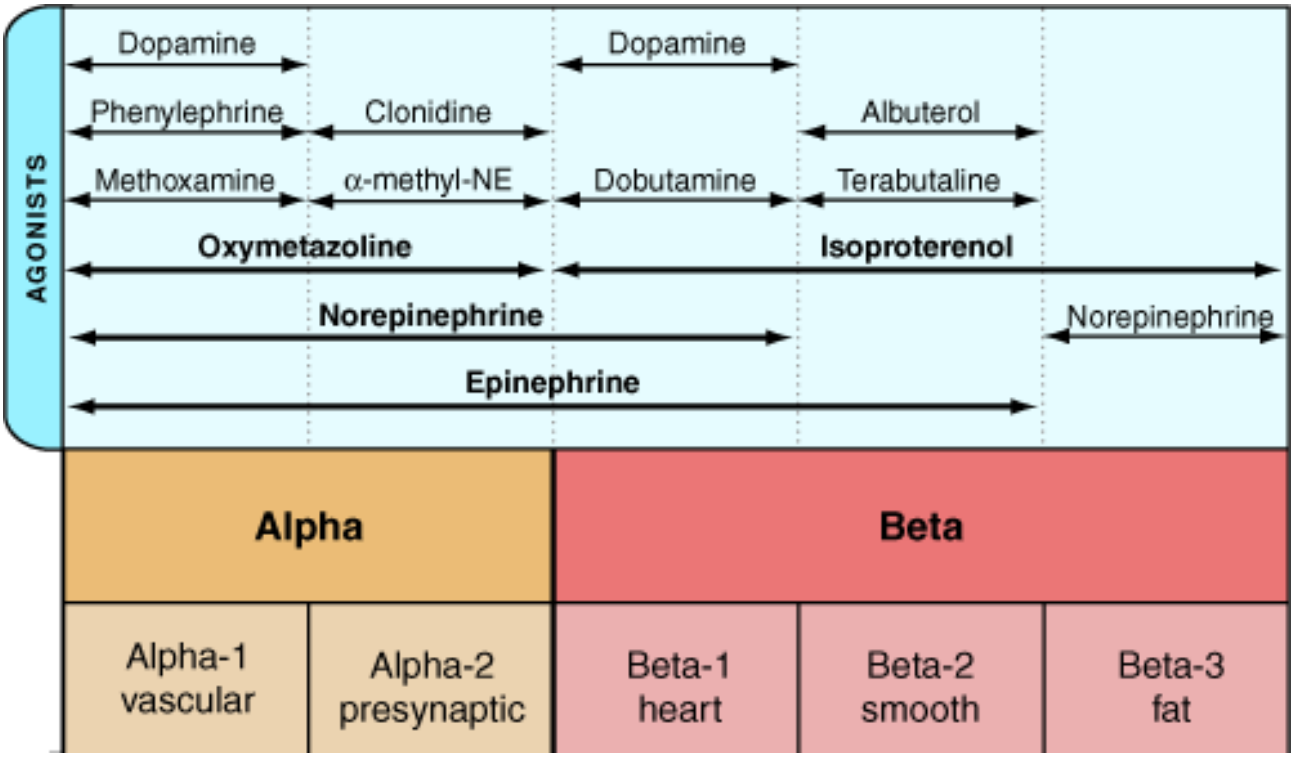
Agents specifically indicated for nasal decongestion:

Pseudoephedrine, Naphazoline, Oxymetazoline, Phenylephrine

Agents specifically abused in sports: Ephedrine, Amphetamine

Drugs that are used as hemostatics along with local anesthatics:

(α_1) agonists: Epinephrine, Norepinephrine, Phenylephrine



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