PHARMACOLOGY OF ANS
part 2

General Pharmacology
M212

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Lecture 14 handout

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Passion 2018

	Catecholamines	Noncatecholamines
Drugs	Epinephrine, Norepinephrine, Isoproterenol, Dopamine	Phenylephrine, Ephedrine, Amphetamine
Potency in activating adrenergic receptors	High	Less
Inactivation (metabolism) rate	Rapid (shorter $T_{1/2}$	Slower (longer $T_{1/2}$)
Inactivation enzymes	COMT	No effect of COMT
	MAO	Poor effect of MAO
Oral	Ineffective	effective
CNS penetration	Poor, but have effect (e.g. anxiety, headache and tremor(	High

Catecholamines are given SC and not orally, even giving them in an iv is dangerous because it could cause atrial fibrillation and death

At low doses epinephrine will stimulate B receptors B1 (causes positive inotropic and chronotropic effect so results in tachycardia, so they can be used in situations like bradycardia of cardiac arrest HR less than 60. Keep in mind this happens by affecting the SA node) and B2 (causes vasodilation at low doses)

And stimulates the A receptors at higher doses will cause vasoconstriction, contradictory actions

The final effect is the sum of both effects together

The final effect will decrease the renal resistance and generally all blood vessels

Here the systolic pressure will increase (The pressure after the contraction of both ventricles which depends on the cardiac output proportionally

So but why does the output increases ? Due to the increase in HR and contractile force because of B1 stimulation

the diastolic pressure decreases for a patient after epi, why ? (the pressure after relaxation of the ventricles) because diastolic pressure depends mainly on the venous return how many volumes return and on the blood vessel resistance

So the accumulative vasodilation affect will affect that resistance of the blood vessels and thus lower the blood pressure

So in the end, the systolic pressure increases while the diastolic decreases

If there is vasoconstriction in renal afferent arterioles the kidneys will shut down

ADRENERGIC AGONISTS

DIRECT-ACTING

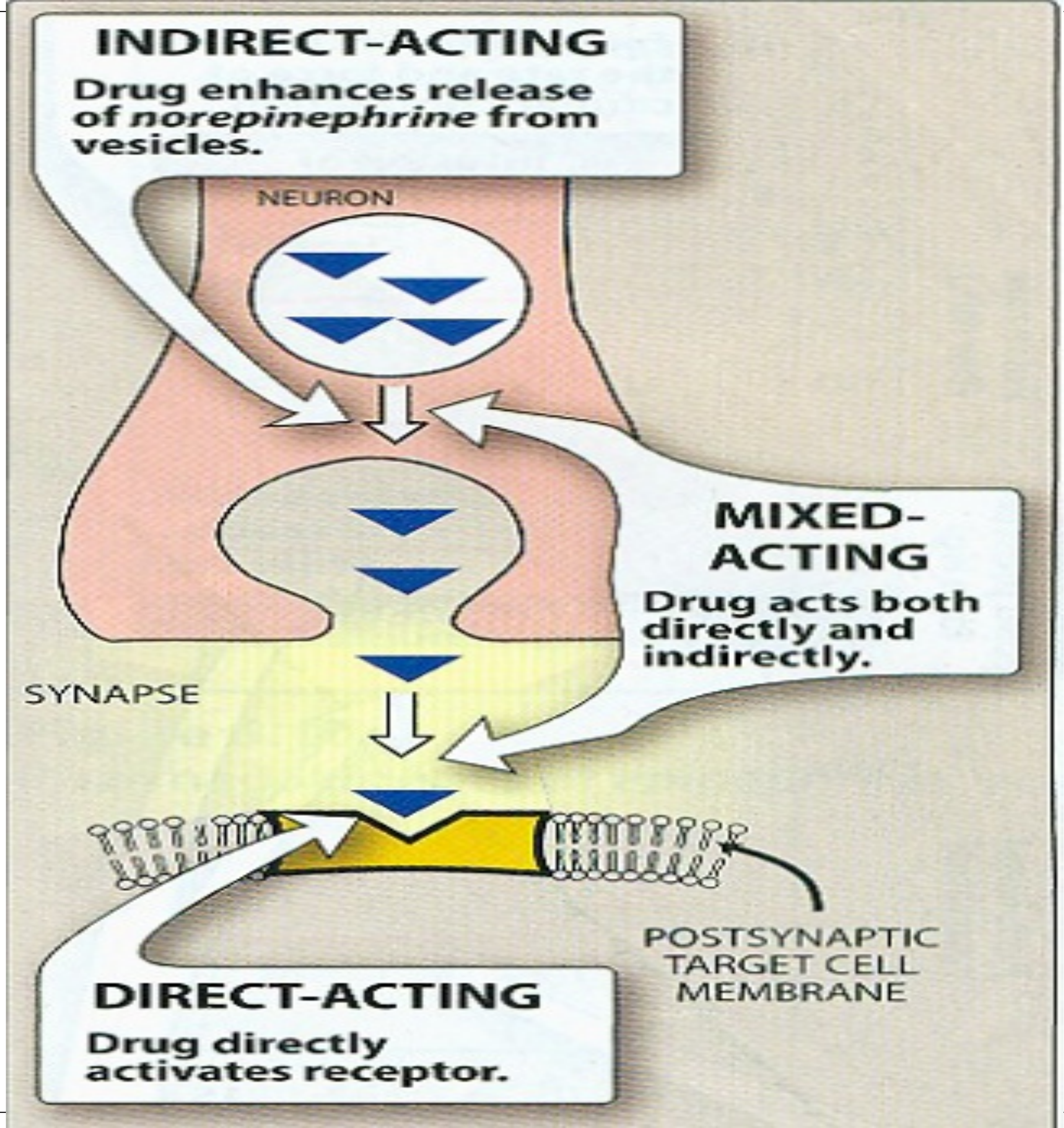
- *Albuterol*
- *Clonidine*
- *Dobutamine**
- *Dopamine**
- *Epinephrine**
- *Formoterol*
- *Isoproterenol**
- *Metaproterenol*
- *Methoxamine*
- *Norepinephrine**
- *Phenylephrine*
- *Piruterol*
- *Salmeterol*
- *Terbutaline*

INDIRECT-ACTING

- Amphetamine
- Cocaine
- Tyramine

DIRECT and INDIRECT ACTING (mixed action)

- Ephedrine
- Pseudoephrine



INDIRECT-ACTING
Drug enhances release of *norepinephrine* from vesicles.
NEURON
MIXED-ACTING
Drug acts both directly and indirectly.
SYNAPSE
POSTSYNAPTIC TARGET CELL MEMBRANE
DIRECT-ACTING
Drug directly activates receptor.

	Epinephrine	Norepinephrine
Release	**Adrenal medulla**	**Major: postganglionic sympathatic neurons** **Minor: adrenal medulla**
Adrenergic receptor	Low dose: β effect (vasodilation(High dose: α effect (vasoconstriction(	Mainly α effect (vasoconstriction) Less effect on β1 and β2 effect
Cardiovascular and kidney Effect	1) +ive inotropic (contractility) and chronotropic (heart rate) action • Increase renin release ! vasoconstriction • Vasoconstriction and vasodilation of certain vessels • Decrease in renal blood flow • ↑ Systolic & ↓ diastolic BP	• Vasoconstriction for all blood vessels and vasodilation of certain vessels • Initially: +ive inotropic ----?? reflex bradycardia • ↑ Systolic & ↑ diastolic BP
Duration of action	Short	Very short
Therapeutic use	Cardiac arrest	Cardiac shock

I. Direct-acting adrenergic agonist
1. Epinephrine: Action

- ***CVS effect:***

➢ strengthens the contractility of the myocardium (positive inotropic) and increases its rate of contraction (positive chronotropic).

➢ Activates β1 receptors on the kidney to cause renin release ---- angiotensin II --- a potent vasoconstrictor.

➢ constricts arterioles in the skin, mucous membranes, and viscera (α effects).

➢ Therefore, the cumulative effect is an increase in systolic blood pressure, with a slight decrease in diastolic pressure

I. Direct-acting adrenergic agonist
1. Epinephrine: Action

- **Respiratory:**
- causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action).
- Usually not used because it causes severe dilation but could be used in ER cases.
- **Hyperglycemia:** bad side affect
- increased glycogenolysis in the liver (β2 effect),
- increased release of glucagon (β2 effect),
- decreased release of insulin (α2 effect).
- should be given in caution with diabetic patients

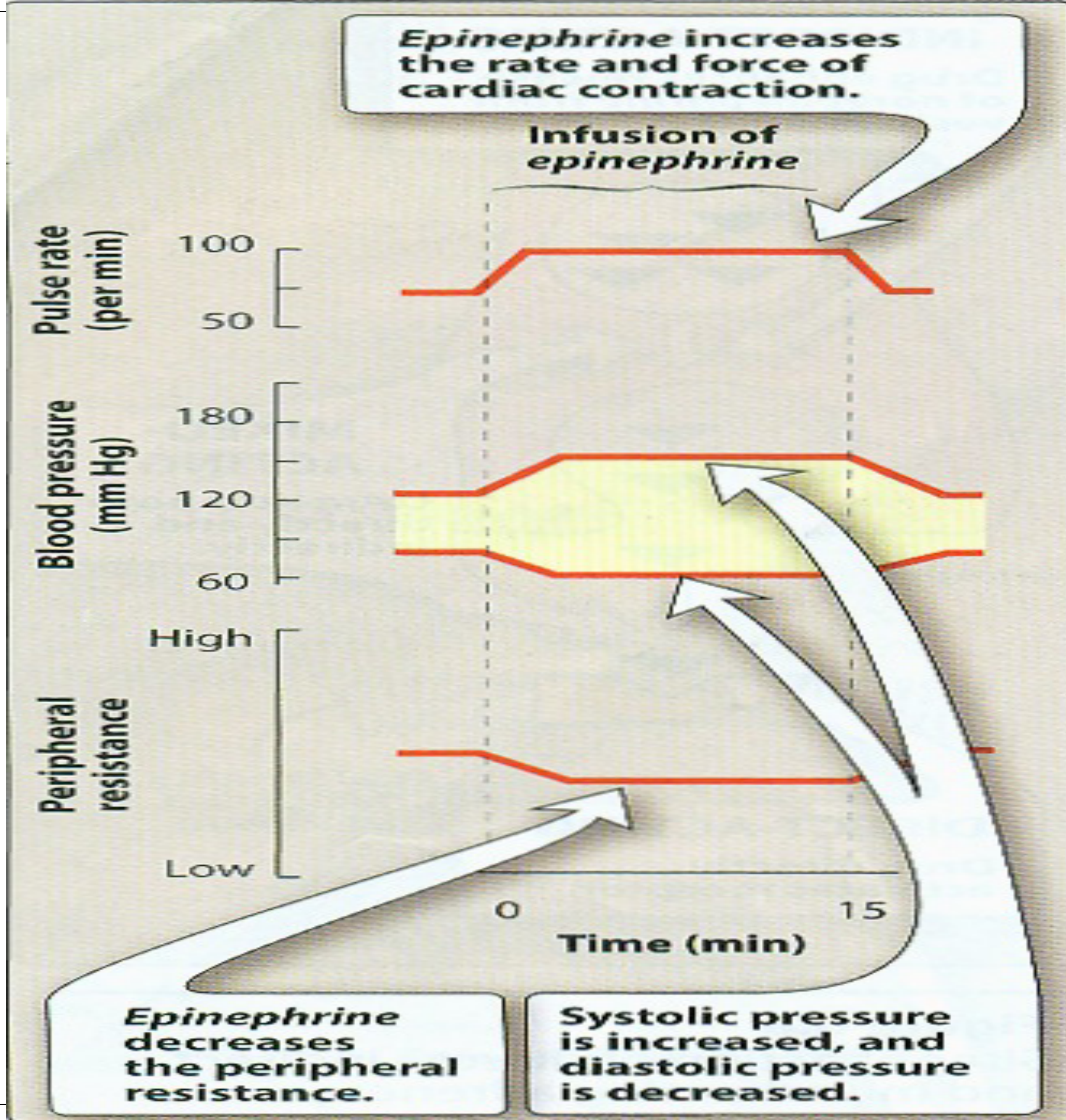
I. Direct-acting adrenergic agonist
1. Epinephrine:

Therapeutic uses

1. Treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice
2. Anaphylactic shock a lot of mediators that will cause severe bronchoconstriction and could cause hypotension because of histamine . Some people they can be allergic to syphalosphorines or penicillins
3. Cardiac arrest
4. Anesthetics not actually anesthetic but given to keep the anesthetic drug more locally by the construction effect ex: mixed with lidocaine

Side effect:

1. Anxiety, fear, tension and tremors
2. Cerebral haemorrhage and stroke if given in a higher dose so the patient should be an in patient
3. Cardiac arrhythmias
4. Pulmonary oedema



Epinephrine increases the rate and force of cardiac contraction.
Infusion of *epinephrine*
Pulse rate (per min)
100
50
Blood pressure (mm Hg)
180
120
60
Peripheral resistance
High
Low
0
15
Time (min)
Epinephrine decreases the peripheral resistance.
Systolic pressure is increased, and diastolic pressure is decreased.

1. Direct-acting adrenergic agonist
2. Norepinephrine

- Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction (α1 effect) of most vascular beds (including kidney) can cause renal failure
- Both systolic and diastolic blood pressures increase
- Norepinephrine is used to treat cardiogenic shock
- Not first line medicine
- There are other medicines that are better for the kidney, one that affect the dopamine receptors in the kidney
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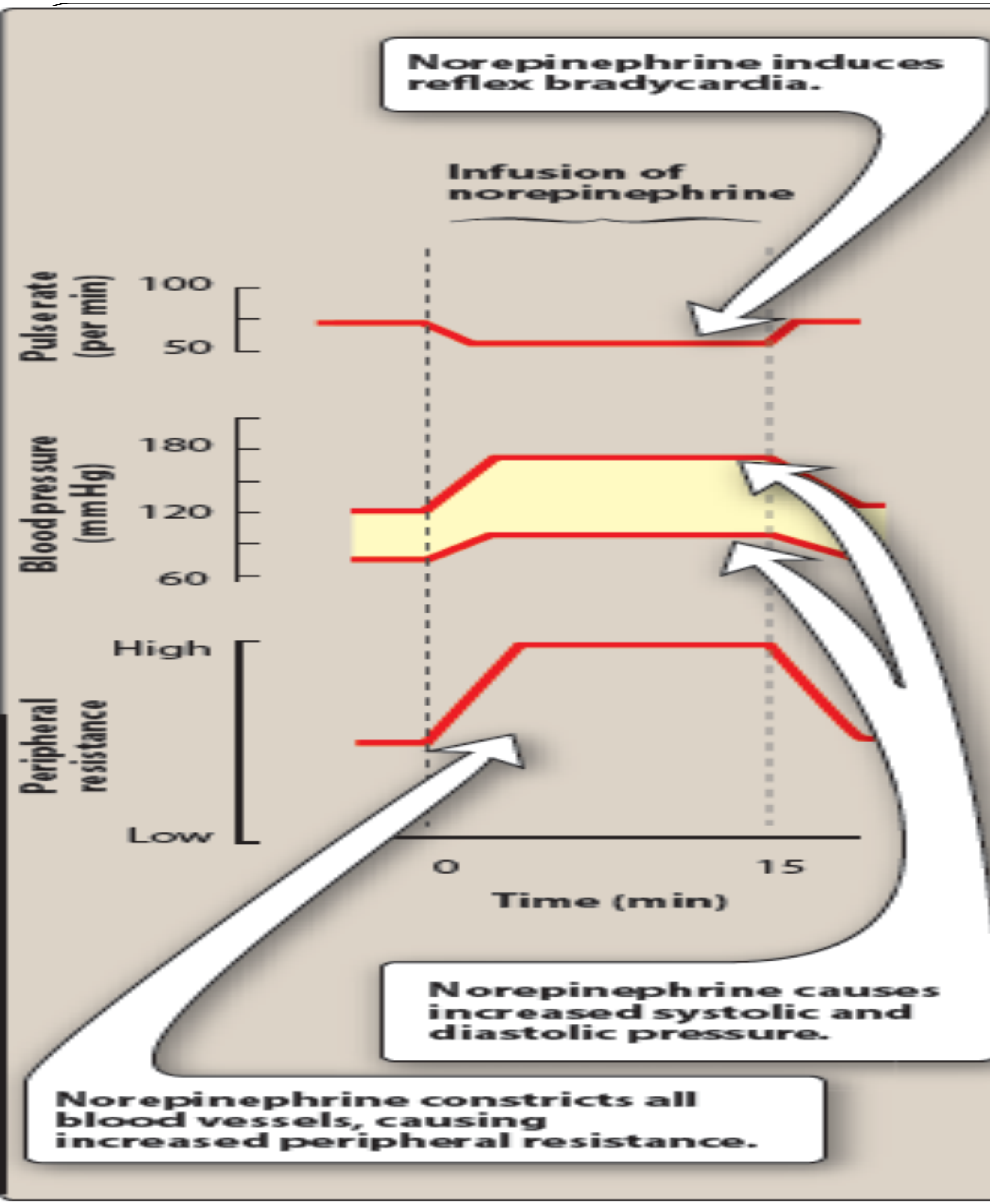


Now let's talk about norepinephrine it works mostly on Alpha receptors so it increases the blood pressure by vasoconstricting the vessels.

This can be very important in specific cases like shock including cardiogenic shock and septic shock or dehydration shock

Keep in mind that a shock means sudden decrease the blood pressure which also causes severe bradycardia

The norepinephrine will cause an increase in the systolic and diastolic blood pressure so reflex bradycardia will occur

Keep in mind here that B receptors of the heart are not involved

I. **Direct-acting adrenergic agonist**

3. Dopamine

- Dopamine stimulates: $\alpha 1$ & $\beta 1$ more selective adrenergic, D1 & D2 those are the opposite of alpha 1 and causes vasodilation in kidneys
- activate dopaminergic receptors, thereby increasing blood flow to the kidneys (vasodilation)
- Dopamine actions:
  - Cardiovascular: +ive inotropic and chronotropic effect ($\beta 1$ effect)
  - vasoconstriction (high dose at $\alpha 1$)
  - Renal and visceral: vasodilation (dopaminergic receptor effect)
- **Uses: Dopamin**e is the drug of choice for cardiogenic shock ?? Why??

I. **Direct-acting adrenergic agonist**

- **4.** Dobutamine not given for shocks because it does not work on the alpha so no increase in BP
  - β1-receptor agonist ! ↑ heart rate without affecting blood vessels
  - Therapeutic use: in congestive heart failure measured by ejection fraction, how much blood is ejected in comparison with pre ejected volume
  - The first line med here is dioxin and the second is dobutamine
  - S.E: atrial fibrillation

5. Clonidine causes obesity

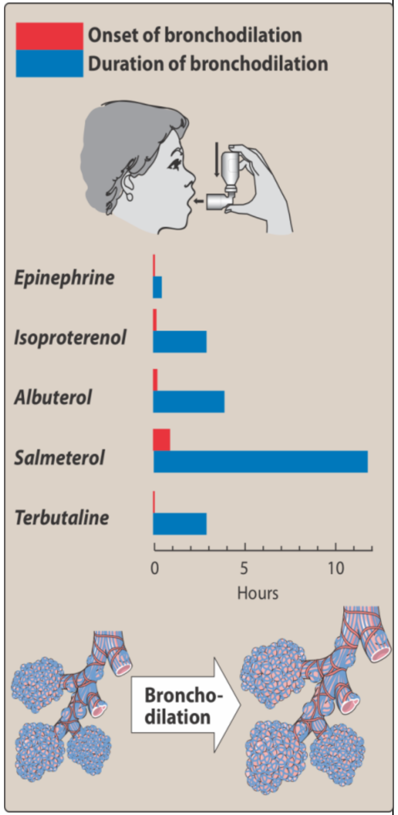
- α2-receptor agonist. Inhibit sympathetic, the efficacy is 0 it just blocks
- Acts centrally by decreasing sympathatic outflow ! lower BP

I. Direct-acting adrenergic agonist

Short acting: Albuterol , terbutaline, inhalers

Long acting: Salmeterol and formoterol orally and given at night to control night asmtha

- **β2 agonists** used primarily as bronchodilators
- administered by **inhaler** for asthma
- Fast onset of action
- Ventolin has no max dose it is a patient oriented drug dosage



I. Direct-acting adrenergic agonist

- **Phenylephrine and Oxymetazoline:**
- $\alpha 1$-receptor agonist
- Used locally to induce vasoconstriction:
- Nasal spray: decongestant (may cause burning of the mucosa and sneezing). Should not be used for more than 3 days because it causes tolerance

II. Indirect-acting adrenergic agonists

1. Amphetamine basic, causes sensitization, kebtagon and used for adhd (a disorder with lower neurotransmitter in the brain) 🧠 keep in mind this is over stimulating for all neurotransmitters dopamine and nore and epi and this causes neuronal damage that is irreversible

stimulants of the CNS

MOA:

Blockade of norepinephrine uptake and enhances its release ! indirect stimulate α1 and β1 receptor agonist

Centrally: stimulatory action ! drug abuse

increase blood pressure significantly by α1-agonist

β-stimulatory effects on the heart.

Therapeutic uses: attention deficit hyperactivity disorder (ADHD, and appetite control the drug is retaline

If taken and causes headache or appetite loss it should be stopped immediately because it causes stroke

II. Indirect-acting adrenergic agonists

2. Cocaine is drug of abuse and it is a stimulant, and so is caffeine, caff efficacy is 30 percent

When adrenaline is stimulated there is no junction between it and dopamine so it causes euphoria

MOA:

- Blockade of norepinephrine uptake !
- sympathatic activity by working indirectly on α1 and β receptor agonist
- Centrally: stimulatory action ! drug abuse
- So: prolongs the CNS and cause intense euphoria

III. MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine and pseudoephedrine **similar to phenylephrine and oxymetazoline**

- MOA: release stored norepinephrine from nerve endings
- directly stimulate both α and β receptors.
- α1-agonist that constricts the nasal mucosa, thereby decreasing airway resistance.
- **Used as a nasal decongestant**
- **High side effect it taken orally**

DRUG	RECEPTOR SPECFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Treatment of open-angle glaucoma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of congestive heart failure

CATECHOLAMINES

- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

NONCATECHOL-AMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally

Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Methoxamine	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Metaproterenol	$\beta_2 > \beta_1$	Treatment of bronchospasm and asthma

Orally

NONCATECHOL-AMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally

Albuterol *Pirbuterol* *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine weight loss abuse	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	Treatment of asthma As a nasal decongestant Raise blood pressure