**بسم الله الرحمن الرحيم**

احب ان انوه عن عدة أشياء في هذه المذكرة من هذا الفصل

الشي الاول دعوني اعرفكم على طريقة المذكرة

بداية بدأنا بأخذ كل ريسبتور واسهبنا في الحديث عن عمله

في هذه المذكرة بالذات وضعنا الادوية التي في حال اتصلت مع الريسبتور تعمل العمل المذكور في كل ريسبتور

ما اريده منكم : عند ذكر كل دواء ووضع الريسبتور الذي يعمل عليه .. رجاءا" ان تقوموا بمراجعة الريسبتورز

وعملها التي في المذكرة الاولى

نفس الكلام سيطبق بالنسبة للبلوكرز .. وهو اننا سنضع عملها على كل سستم في العام وعند ذكر كل بلوكر يجب

مراجعة العام

الشي الثاني وهو لطالما سقط سهوا

احب ان اشكر ***الاخ محمد الرويشد*** الذي هو عضو في التيم

نأسف لسقوط الاسم ولكن نسخة المقدمة كانت قديمة وسيتم التعديل عليها

الشي الثالث نحن جدا" آسفون على تأخير المذكرة

ولكن احببنا ان تظهر على اكمل صورة

والقادم اعظم ☺

لا تحرمونا من دعائكم في هذه الايام الفضيلة

◙ **Note :**

- ***What is the difference between $\alpha_1$ and $\alpha_2$ adrenoceptors?***
  - $\alpha_1$ is post-synaptic while $\alpha_2$ is pre-synaptic .
  - $\alpha_1$ is stimulatory through Gq while $\alpha_2$ is inhibitory either through $K^+$ channels or through Gi protein ) .

- ***$\alpha_2$ stimulation cause decreased Norepinephrine release (autoregulatory mechanism). Very important effect Why?*** Because although Epinephrine and NE do not have as pronounced effects as does Ach. , if they were lift unchecked they may cause excessive stimulation with catastrophic effects.

- $\alpha_2$ stimulation may decrease salt & water flux into the lumen of intestine

- In Conducting system : increase conduction velocity **(+ve dromotropic)** via $\beta_1$
- Increase ectopic beats ( if there was excessive stimulation ) .

- $\beta_2$ stimulation causes relaxation of the ciliary muscle leading to accommodation for far vision.

- **$\beta_2$ stimulation causes increased production of aqueous humor .Can we use β-adrenergic agonists for glaucoma?**
  No, because it will complicate it and lead to increase intra-ocular pressure. So, we use β-antagonist to treat glucoma .

# Sympathmimetic drugs

## DRICT ACTING

- Epinephrine
- Norepinephrine
- Isoproterenol
- Dopamine
- Dobutamine
- Phenylephrine
- Clonidine
- Metaproterenol
- Terbutaline
- Salbutamol
- Salmetrol and Formoterol
- Ritodrine

## INDIRECT ACTING

- Amphetamine
- Methamphetamine
- tyramine

## MIXED ACTING

- Ephedrine
- pseudoephedrine

Very important figure ☺

# specific sympathomimetic drugs classification :

## ♣ Direct acting adrenergic agonists:

Direct acting drugs bind to the receptors, so specificity of action is a possibility.

Indirect acting drugs don't bind to the receptors, but act by releasing stored NE. this means that their action are not specific .

### Epinephrine (Adrenaline)

stimulate both α and β receptors (non-selective).

EP is released from adrenal medulla 80% and in certain areas of the brain

$T_{1/2}$ = 2 – 5 min

**Does PK of Epinephrine different from NE?** The answer is ( NO )

**when u think about sympathomimetic drugs put in ur mind 3 things**
- work on which receptor
- is it a catecholamine or not
- direct or indirect

**pharmacokinetic :**

» rapid onset , short duration of action
» given IV, S.C endotracheal tube , inhalation, topically on eye.
» oral administration is not effective, because it is inactivated by intestinal enzymes
» excreted in urine ( metabolized by COMT and MAO )

**pharmacological actions** ( effects on α and β receptors ) [ so u must revise their works]

**clinical uses :**

**1.** Bronchospasm by acting on **$\beta_2$** to cause **bronchodilation**
**2.** Anaphylactic shock

◙ **Note :**
**Anaphylactic shock** is a severe allergic reaction release histamine (vasopressin) which cause sever hypotension. Common triggers include bee and wasp stings, nuts, shellfish, eggs, latex and certain medications, including penicillin.

Symptoms include burning and swelling of the lips and tongue, difficulty breathing (like in an asthma attack), red, itchy or blistered skin, sneezing, watery eyes, nausea and anxiety. Anaphylaxis requires urgent treatment in hospital.

Anaphylaxis requires urgent treatment in hospital. People at risk should always carry an emergency anaphylaxis treatment kit that includes adrenaline which ↑ systolic blood pressure.

**3.** Acute asthma (by S.C) to act on $\beta_2$ receptors to cause bronchodilation

◙ **Note :**

◦ why for acute attack of asthma ? → because of rapidity of action.
◦ Now it is not commonly used because of its side effects (tachycardia and arrhythmia)

**4.** Glaucoma

2% topically to reduce IOP in open angle glaucoma ( reduces the production of aqueous humor by VC of the ciliary body blood vessels )

**5.** Cardiac arrest

◙ **Note :**

A.V block → cardiac arrest
treat'em with either electrical shock or adrenalin injection

**6.** in anaesthesia with local anesthetic (LA)

a- ↑ the duration of LA ( by VC at the site of injection)
b- ↓ the dose of LA
c- ↓ the side effects of LA
d- control blood oozing ( hemorrhage ) of capillary blood ( local haemostatic effect by VC)

◙ **Note :**

why we don't use in the epinephrine for nasal decongestion and mydriatic ? because it has a short duration of action , so in case of nasal decongestion it will rebound congestion .

**adverse effect :**

**1.** CNS : anxiety, fear, tension, headache, tremor (poorly penetrate CNS)
**2.** hemorrhage : cerebral hemorrhage as a result of ↑ B.P

◙ **Note :**

◦ remember the epinephrine will elevate the systolic BP , so if he has hypertension he will dead after supplying him with this drug .
◦ there is Exception : when we give very high I.V. it will increase diastolic BP through α1 by causing vasoconstriction .

**3.** cardiac arrhythmias
**4.** pulmonary edema
**5.** hyperglycemia
**6.** interactions
a- hyperthyroidism
- enhanced CVS action in patients ( ↑ H.R)

b- cocaine :
- epinephrine produces exaggerated CV actions as cocaine prevent reuptake of catecholamines into adrenergic neurons .

## Norepinephrine

- NE is a neurotransmitter released from the postganglionic sympathetic fiber in most organs
- It is also released from the adrenal medulla (20% of medulla secretion)

**Sites of metabolism :**

- In adrenergic nerves
- 80% by MAO in presynaptic nerve terminals after reuptake (This is very important clinically)
- If MAO is inhibited, NE will be reuptake but not metabolized, leads to release of NE again
- 15% by COMT in postsynaptic membrane (This is not important clinically)
- 5% reach the blood and metabolized In the Liver

**Pharmacokinetics :**

- $T_{1/2}$ of NE = 2 – 3 min
- Very short because it has rapid metabolism
- oral administration is not effective, because it is inactivated by intestinal enzymes
- act on α and β but mainly on α adrenoceptor
- ↑ peripheral resistance and both systolic and diastolic BP, So, in shock, it will increase BP
- reflex bradycadia

**reflex bradycadia :**
norepinephrine causes constriction of all major vascular beds. This, in turn, causes an increase in resistance and pressure. The increase in blood pressure causes stimulation of the baroreceptors which cause reflex increase in parasympathetic output (vagal discharge) to the heart, which acts to slow the heart down. Therefore, heart rate often decreases after administration of norepinephrine in spite of direct activation of $\beta_1$ receptors.

**Clinical uses :**

Note: NE is not commonly used in clinical practice like Epinephrine, However it can be used in:

- IVI to treat shock (PVR and BP )

metaraminal is preferred as it does not reduce blood flow in kidney.

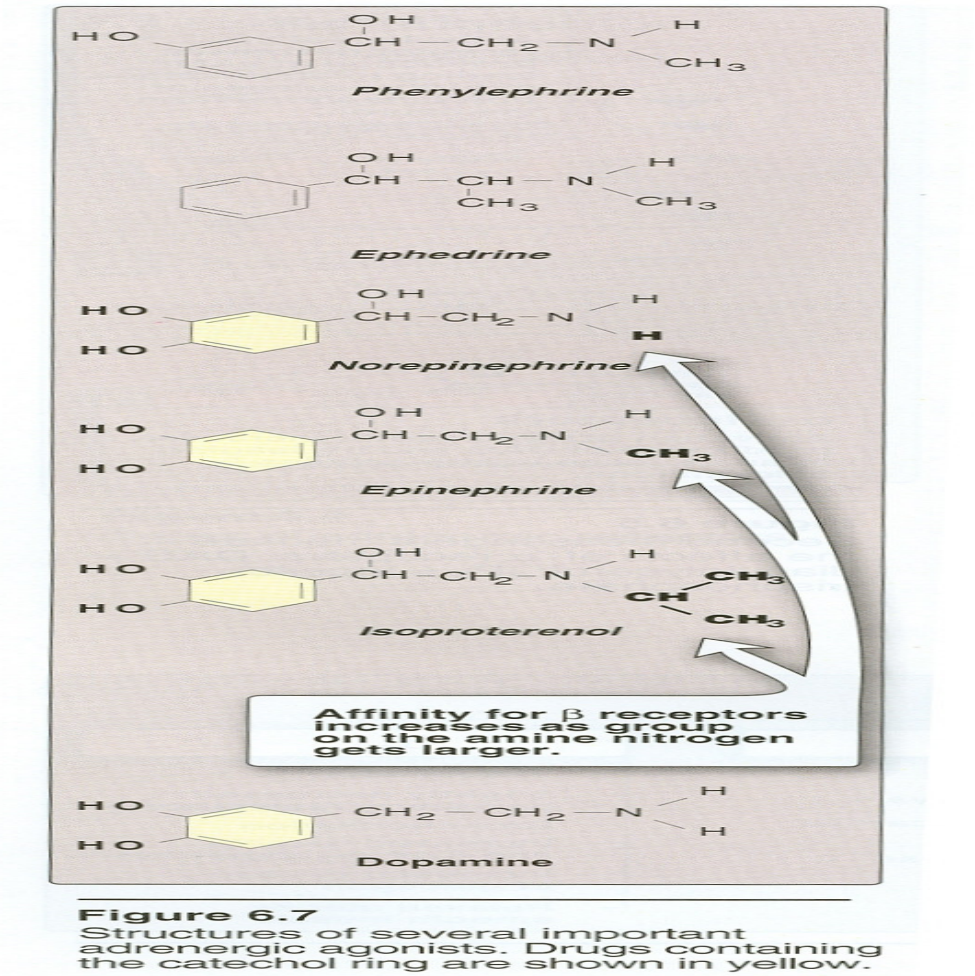


**Figure 6.7**
Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.

**There is a rule that you should know it :**
When you add $CH_3$ --------- increase the affinity to $\beta_2$ agonist
So, isopreterenol has 2 $CH_3$ ------ most effect on $\beta_2$

**What are the main differences between Epinephrine and NE?**
* In normal dose epi will cause increase in systolic & slight Decrease in diastolic BUT Nor epi causes increase in both Diasolic & Systolic .

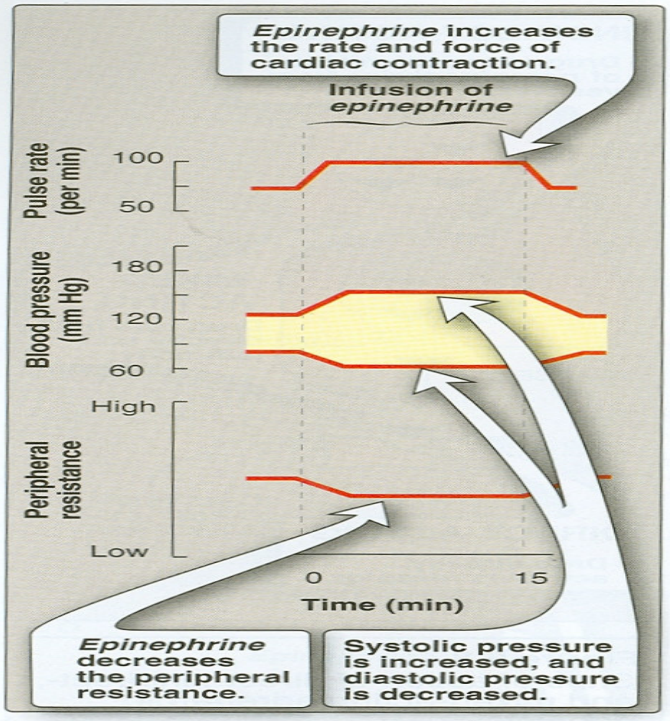


**Figure 6.9**
Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

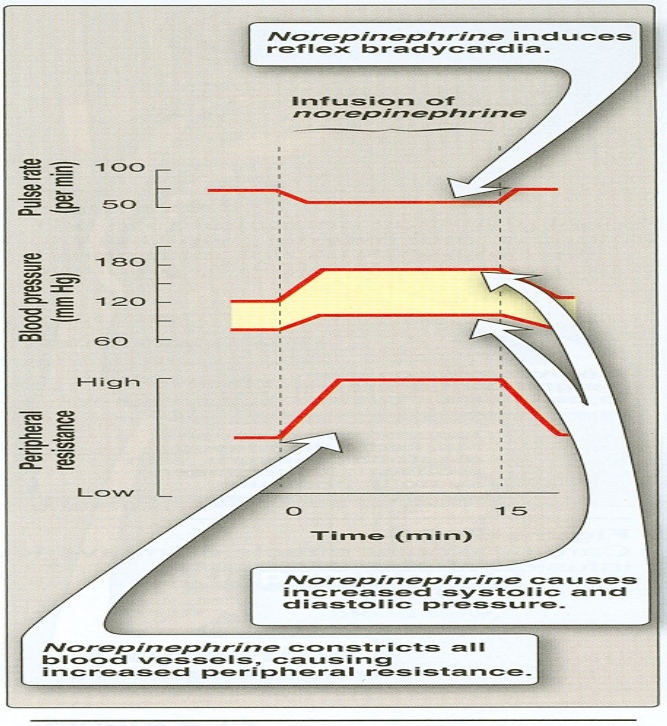


**Figure 6.11**
Cardiovascular effects of intravenous infusion of *norepinephrine*.

## isoproterenal ( isoprenaline )

- **synthetic** adrenoreceptor agonist
- stimulates both $\beta_1$ and $\beta_2$ (u have to revise the action on these receptor in the previous booklet) , with no effects on a adrenoceptors
- $T_{1/2}$ = 5 – 7 min
- Like all catecholamines, It is given parenterally (not orally)
- The I.V must be given carefully because the overdoses cause cardiac arrest

**clinical use :**

**1.** used in A.V ( atrioventricular ) block or cardiac arrest
↓ diastolic BP and mean arterial pressure

N.B. cardiac arrest means : complete cessation of heart's activity. While heart block means : partial or complete inhibition of the spread of conduction of the electrical impulse from the atria to the ventricles

**2.** acute attack of asthma ( inhalation) takes parenterally, sublingual.

It is no longer used to treat the bronchial asthma because of it's side effects on the heart

It's only used now to reverse the heart block which is produced by overdoses of β – blockers

**adverse effect:** as epinephrine

it has nothing with cerebral hemorrhage

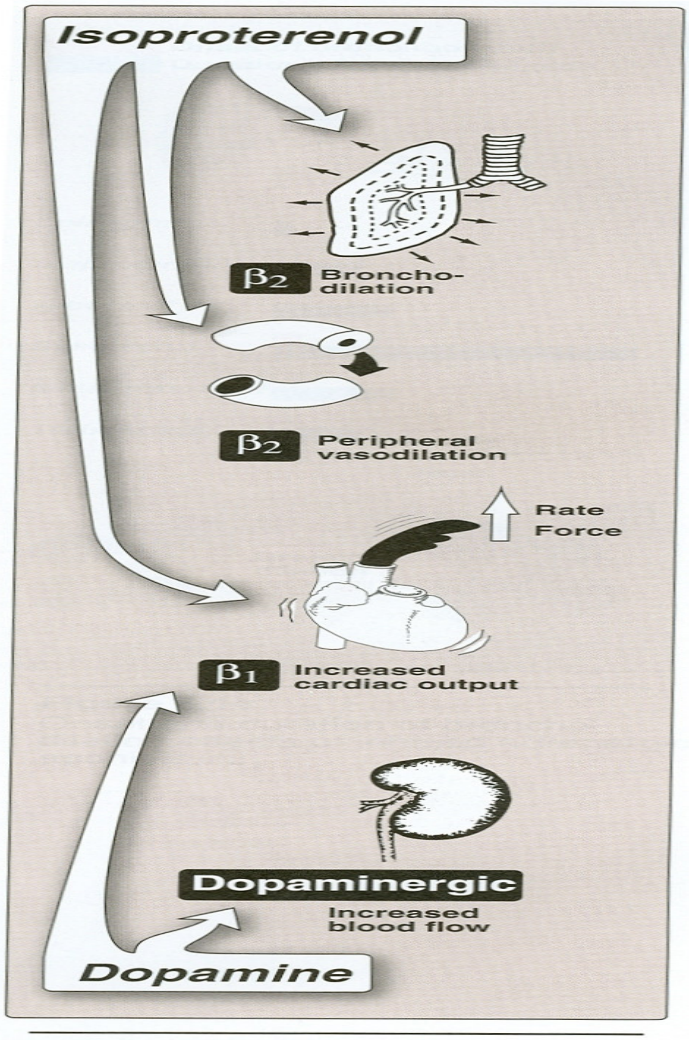


**Figure 6.13**
Clinically important actions of *isoproterenol* and *dopamine*.

## Dopamine

» **natural**
» immediate metabolic precursor of norepinphrine
» occurs in the CNS in the basal ganglia also in adrenal medulla
» direct activation of adrenoceptors including α , β , $D_1$ and $D_2$ dopaminergic receptors
» occur in mesenteric and renal vascular bed → VD
» stimulation of Dopamine → vasodilatation of all visceral vascular BV including kidney
» Like all catecholamines, It is given parenterally only (not orally)

» It doesn't cause tolerance

» $T_{1/2}$ = 3 – 5 min

» Metabolized by either Converted to NE in adrenergic neurons or By MAO in the Liver

**pharmacological action :**

1. CVS : +ve ionotropic and chronotropic ($\beta_1$) and V.C (α receptor) → hypertension
2. renal and visceral VD ( dopamine receptors) ↑ renal blood flow and other viscera

**therapeutic uses :**
1. shock → IVI ↑ BP and improves blood flow to viscera
2. cardiac heart failure (+ve ionotropic) in acute attack

In small dose of DA (=< 5ug / Kg / min by I.V infusion) Renal dose:

- It will stimulate DA–receptors only → It will cause vasodilatation (VD) in:
- Renal vascular bed, Cerebral vascular bed, Coronary vascular bed, Mesenteric vascular bed

**Therefore, it is useful in treatment of shock to save these vital organs from hypoxia (also see Dobutamine) (No evidence)**

**N.B** : At higher doses, VD effect of DA – receptors is masked by the VC effect of $\alpha_1$– receptors, therefore No longer small dose of dopamine is used

In medium dose : (5-15ug/Kg/min by I.V infusion) Cardiac dose (This is the commonly used dose) → It will stimulate $\beta_1$ – receptors to cause increase HR, CO and BP

So it will use to treat hypotension shock & cardiogenic shock

In high dose of DA (> 15ug / Kg / min by I.V infusion) :

- It will stimulate α1 receptors (direct + Via release of NE) to cause VC leading to increase BP and decrease organ perfusion

What is the effect of Dopamine on Bronchioles? Answer : No effect

**adverse effects:**
- nausea, hypertension, arrhythmia, angina

## Dobutaime:

» Selective $\beta_1$-receptor agonist (synthetic )

» $T_{1/2}$ = 10 – 15 min

» It is metabolized in the liver by oxidative deamination

» There is tolerance to its action (Opposite to Dopamine)

» Given only parenterally (not orally)

**Uses :**
acute attack of CHF (congestive heart failure) by IVI
- It causes increases in CO with minimal effect on HR, so we use it as Inotropic agent for Heart Failure; in septic and shock (with pulmonary congestion).

**Adverse effects :**

- Cardiac arrhythmias (less effect than Dopamine)
- Anginal attacks

**Can you make comparison between Dopamine and Dobutamine?**

## Phenylephrine:

- Acts primarily on α mainly $\alpha_1$ receptors
- PK: not-catecholamine and thus not metabolized by COMT
- It has longer duration of action than other catecholamines
- VC → ↑ both systolic and diastolic BP
- Has no effect on the heart
- Reflex bradycardia

**Used**
- topically on the nasal mucous membrane as nasal decongestion
- Also as ophthalmic solution for mydriasis **to examine the fundus of the eye**
- It acts on $\alpha_1$ – receptors in the radial dilator pupillary muscle
- As VC is used to rise BP
- As a vasopressor agent in case of hypotension
- Used to terminate episodes of supraventricular tachycardia (**paroxysmal tachycardia)**

**Adverse effects :**
Hypertension, headache, cardiac irregularities (arrythmia )

## Clonidine

- Is an $\alpha_2$ agonist
- Used in essential hypertension to lower BP (action on CVS )
- Used to minimize the symptoms of withdrawal from opiates as benzodiazepam
- Centrally inhibits sympathetic vasomotor, It acts centrally at presynaptic $\alpha_2$-adrenoceptor. This leads to decrease in NE release and to decrease in TVR.

**Adverse effect :**

- Dry mouth
- Sedation
- Psychological effect anxiety depression contraindicated

## Metaproterenol

- Is not a catecholamines (long acting )
- Not metabolized by COMT
- Given orally or by inhalation
- Act on $\beta_1$ and $\beta_2$ (mainly on $\beta_2$-receptor)
- Used to treat chronic asthma and bronchospasm

## Terbutaline

- Short acting $\beta_2$ agonist
- By inhalation to treat acute asthma
- Produce less cardiac stimulation

## Salbutamol:

- It is $\beta_2$ – selective agonist ( if in the question he said relative selective agonist its true because it has some effect on $B_1$ )
- Can be used orally, IV and by inhalation

**Clinical Uses :**

- Formulations: (Tablets; Syrup; Injection; solution and Inhalation)
- bronchial asthma by $\beta_2$ stimulation, which leads to relaxation of bronchial smooth muscle and bronchodilation.
- Half life is not long ( not good for nocturnal asthma )
- Treatment of refractory hyperkalemia (I.V)
- Note : Salbutamol have little effect on $\beta_1$ so it causes some tachycardia

## Salmetrol and Formoterol:

- These selective beta agonists, have longer duration of action as compared to Salbutamole.

**Uses:** As inhalors for Noctural B. Asthma Why?

Because of their long half life

## Ritodrine:

- It is another $\beta_2$ – selective agonist but
- It is used to delay premature labour
- $\beta_2$ stimulation leads to relaxation of uterine smooth muscle leading to delay of labour
- This is done to ensure adequate maturation of fetus

**Side Effect of all $\beta_2$-agonists:**

Tachycardia; hypokalemia

Glaucoma

## ♣ InDirect acting adrenergic agonists:

### Amphetamine

- Acts as α and β receptors
- $t_{1/2}$ = 45 – 60 min (long duration of action)
- It is metabolized in the Liver
- Since it is non-catecholamine, it can be given orally
- It is lipid–soluble enough to be absorbed from intestines and goes to all parts including CNS (This leads to CNS stimulation like restlessness and insomnia)
- Marked central stimulatory action ( a mood elevating effect)

  a. attention –deficit hyperactivity disorder of children
  b. narcolepsy (altering effect and improved attention )
  c. appetite control (suppressing effect) as in obesity
  d. contraindicated in pregnancy (teratogenic)

**adverse effects:**

- adrenergic CNS, addiction, hypertension, paranoia, psychosis, tolerance, cardiac arrhythmia, anginal pain.

### Amphetamine-like drugs

Amphetamine is a drug of abuse, that should not be prescribed. However, amphetamine-like drugs can be used for the following conditions:

**In ADHD "Attention Deficit Hyperactivity Disease: (Methylphenidate, Dexamfetamine)**

**In narcolepsy**

Narcolepsy is irresistible attacks of sleep during the day in spite of enough sleep at night Amphetamine-like drugs stimulate the CNS & make the patient awake (Dexamfetamine and Modafinil)

**To suppress appetite**

In very obese persons Amphetamine can act centrally on the hunger center in the hypothalamus to suppress appetite **(Considered as an obsolete use)**

**methamphetamine**

- has a higher CNS effect used as anorexignic

**tyramine**

- formed in fermented food as cheese with MAOI → serious vasopressor effects causing increasing in BP

## ♣ mixed acting adrenergic agonist:

**ephedrine (a plant alkaloid )**

- indirectly acting by releasing stored norepinephrine from nerve endings and,
- directly acts on α and β receptors
- similar to epinephrine but less potent
- not a catecholamine drug, It is non selective adrenergic agonist
- long duration
- CNS stimulant better than epinephrine
- Absorbed well orally
- Penetrates into CNS
- Eliminated unchanged in urine
- ↑ both systolic and diastolic BP (by VC and cardiac stimulation )
- It is not drug of abuse .
- PK almost similar to amphetamine (long t1/2 and goes to CNS)
- does not suppress the appetite
- Used as prophylactic in chronic asthma

**It is no longer used to treated bronchial asthma. Why?**

Non – selective , go to CNS , tachycardia

- Enhance skeletal muscle contractility and improves motor function in myasthenia graivs
- Mild stimulation to CNS → ↑ alertness, ↓ fatigue, insomnia
- Improves athletic performance
- Nasal decongestion
- ↑ BP
- Is useful in treatment of stress incontinence

**Conclusion :**

Ephedrine produces actions similar to Epinephrine but taken orally, however, has some similarities with amphetamine.

## Pseudoephedrine (stereoisomer of ephedrine)

- It is ephedrine derivative which has similar pharmacological activities to the parent (ephedrine) but with short duration of action. Interestingly, It is not controlled drug: OTC (over the counter)
- Used in oral preparation for the relief of nasal congestion
- Less potent than ephedrine in producing tachycardia, hypertension, CNS stimulation
- Used in the treatment of stress incontinence

## Phenylpropranolamine:

- Again it is similar to pseudoephedrine, and was used as decongestant, but it was stopped because it may cause cerebral hemorrhage

## Side – effects of centrally acting sympathomimetics:

**Sympathomimetic means :**

**These drugs can produce sympathatic actions similar to EP and Nor EP**

**They include:**

- ✓ Amphetamine
- ✓ Ephedrine
- ✓ Pseudo ephedrine
- ✓ Phenyl Pro Pranolamine

**They are lipid – soluble and can pass BBB to cause**

- ✓ Insomnia
- ✓ Restlessness
- ✓ Confusion
- ✓ Irritability
- ✓ Anxiety
- ✓ Loss of appetite ( except ephedrine )
- ✓ Hypertension
- ✓ Amphetamine has additional side effect (revise it)

**Selective Adrenoceptor Agonists these drugs include :**

$\alpha_1$ – agonist → Phenyl Ephrine

$\alpha_2$ – agonist → Clonidine, Methylodopa (antihypertension)

$\beta_1$ – agonist → Dobutamine

$\beta_2$ – agonist → Salbutamol, Ritodrine, Salmetrol, Terbutaline

# Clinical applications of Sympathomimetic drugs :

we use **Phenyl Ephrine :**

- ✓ In shock (hypotension → shock)
- ✓ Type of shock include : Hypovolamic shock, Septic shock, Anaphylactic shock
- ✓ Symptoms include :
  - Congestion in the Lung, Heart & Kidney due to VD & V.Per
  - Bronchoconstriction, Hypotension

We use **EP** with steroid and antihistamine to cause:

- ✓ Bronchodilation
- ✓ Increase BP
- ✓ Decongestant
- ✓ Neurogenic shock
- ✓ Cardiogenic shock

We use **DA & Dobutamine** together

All type lead to increases in BP → To reduce BF in certain organs

We use ***Adrenaline*** with local anesthetic for minor surgery in order to:

- ✓ Decrease bleeding
- ✓ Prevent spread of local anesthetic into systemic circulation
- ✓ In paroxysmal tachycardia
- ✓ In bronchial asthma
- ✓ In cardiac arrest
- ✓ For mydriasis
- ✓ For delaying of labor
- ✓ For hyper kinetic children syndrome
- ✓ For narcolepsy