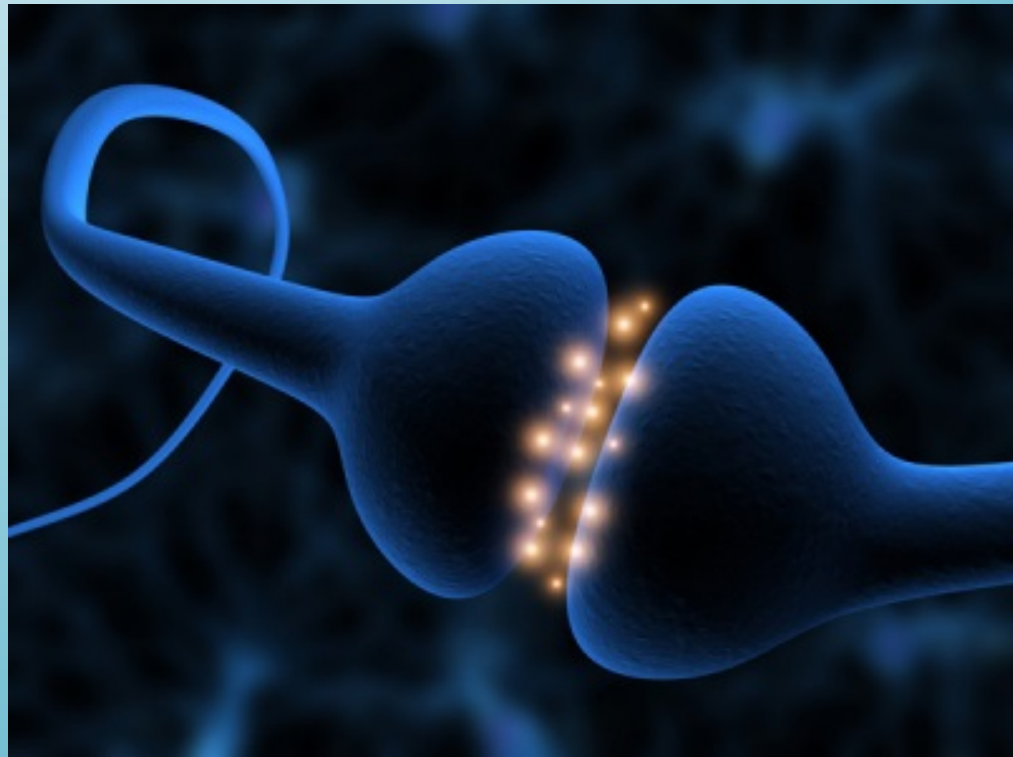


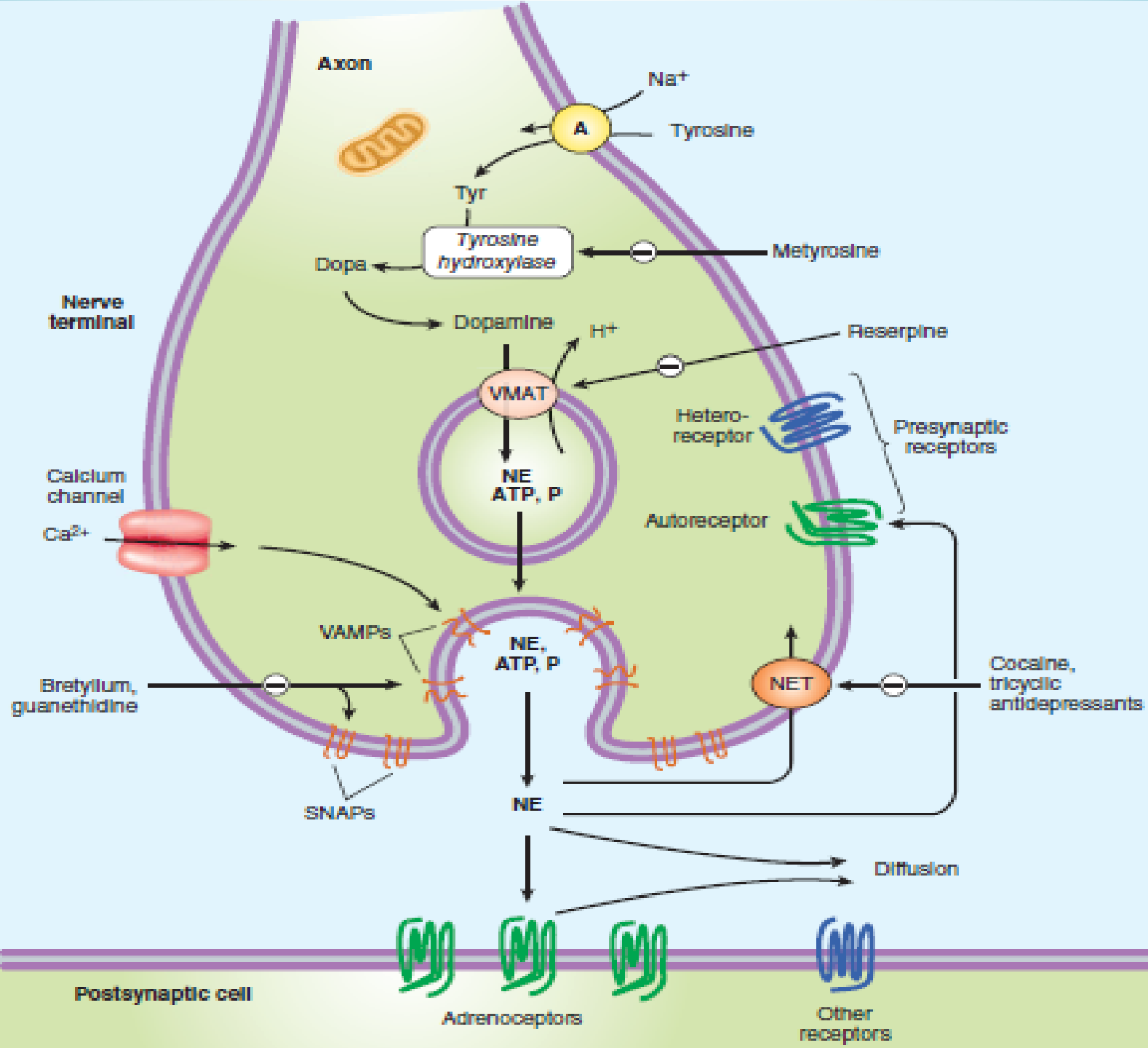
# Adrenergic agonists

*Ahmed Shubbar*



# Adrenergic neurotransmission

- What is the primary neurotransmitter in adrenergic neurons ?
- Adrenoreceptors are typical G-Protein coupled receptors (GPCRs).



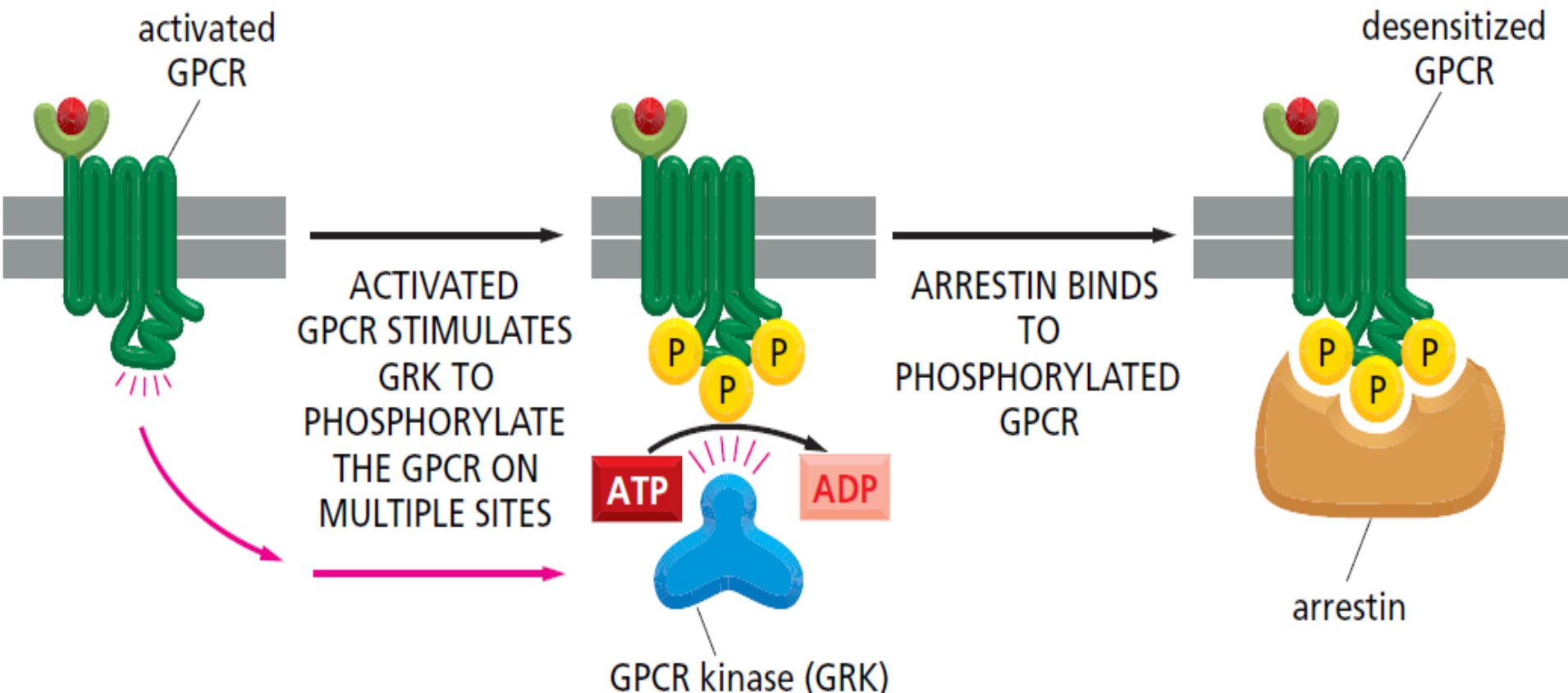
# Molecular Pharmacology of adrenoreceptors

| Receptor                    | G-protein      | Affected enzyme | 2 <sup>nd</sup> messenger |
|-----------------------------|----------------|-----------------|---------------------------|
| $\alpha_1$                  | G <sub>q</sub> | ↑ PLC           | ↑ IP <sub>3</sub> & DAG   |
| $\beta$ , D <sub>1</sub>    | G <sub>s</sub> | ↑ AC            | ↑ cAMP                    |
| D <sub>2</sub> , $\alpha_2$ | G <sub>i</sub> | ↓ AC            | ↓ cAMP                    |

# Adrenoreceptors desensitization

- Occurs after prolonged exposure to catecholamines.
- Also known as tolerance , tachyphylaxis.

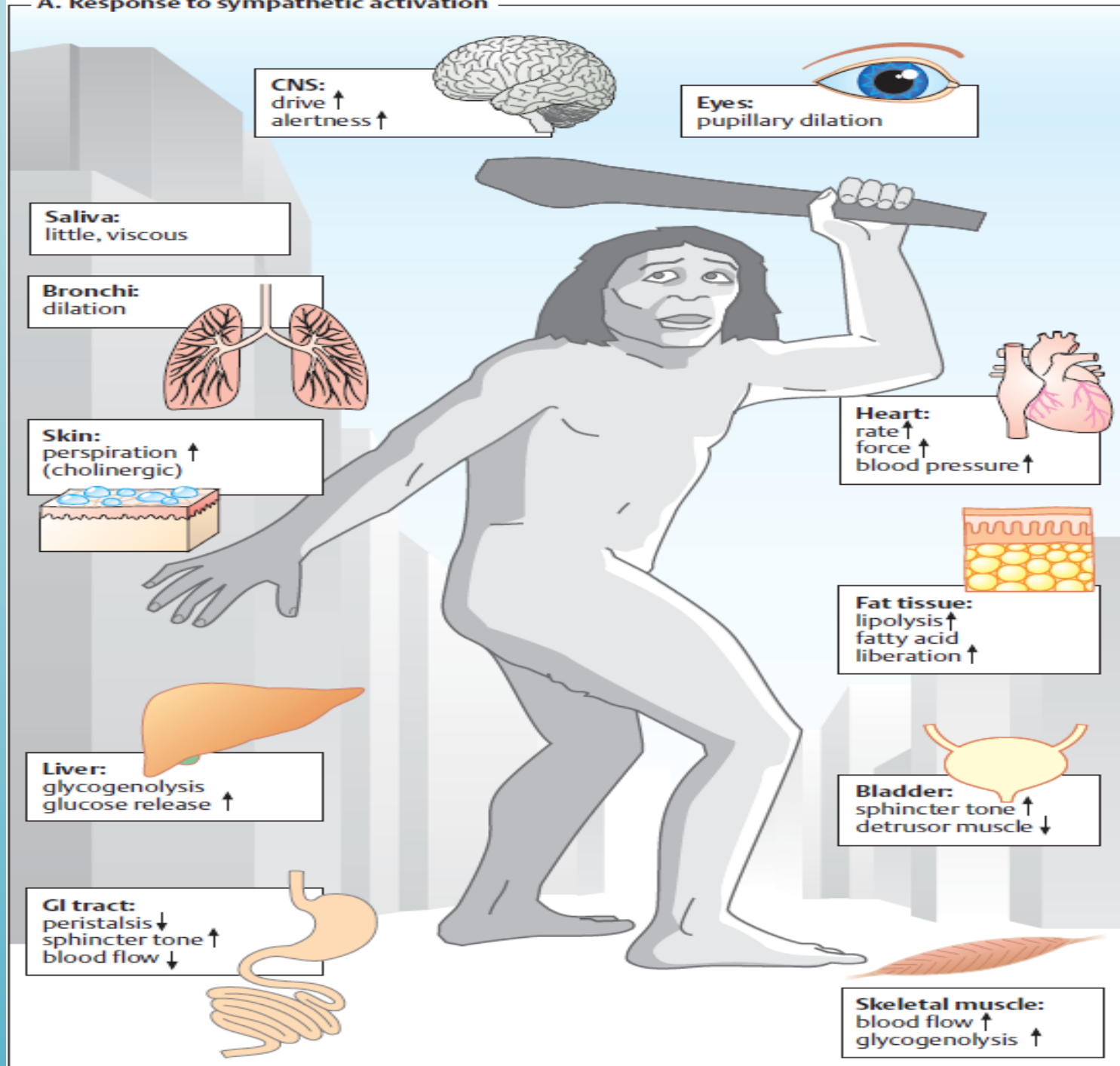
# Mechanism adrenoreceptors desensitization







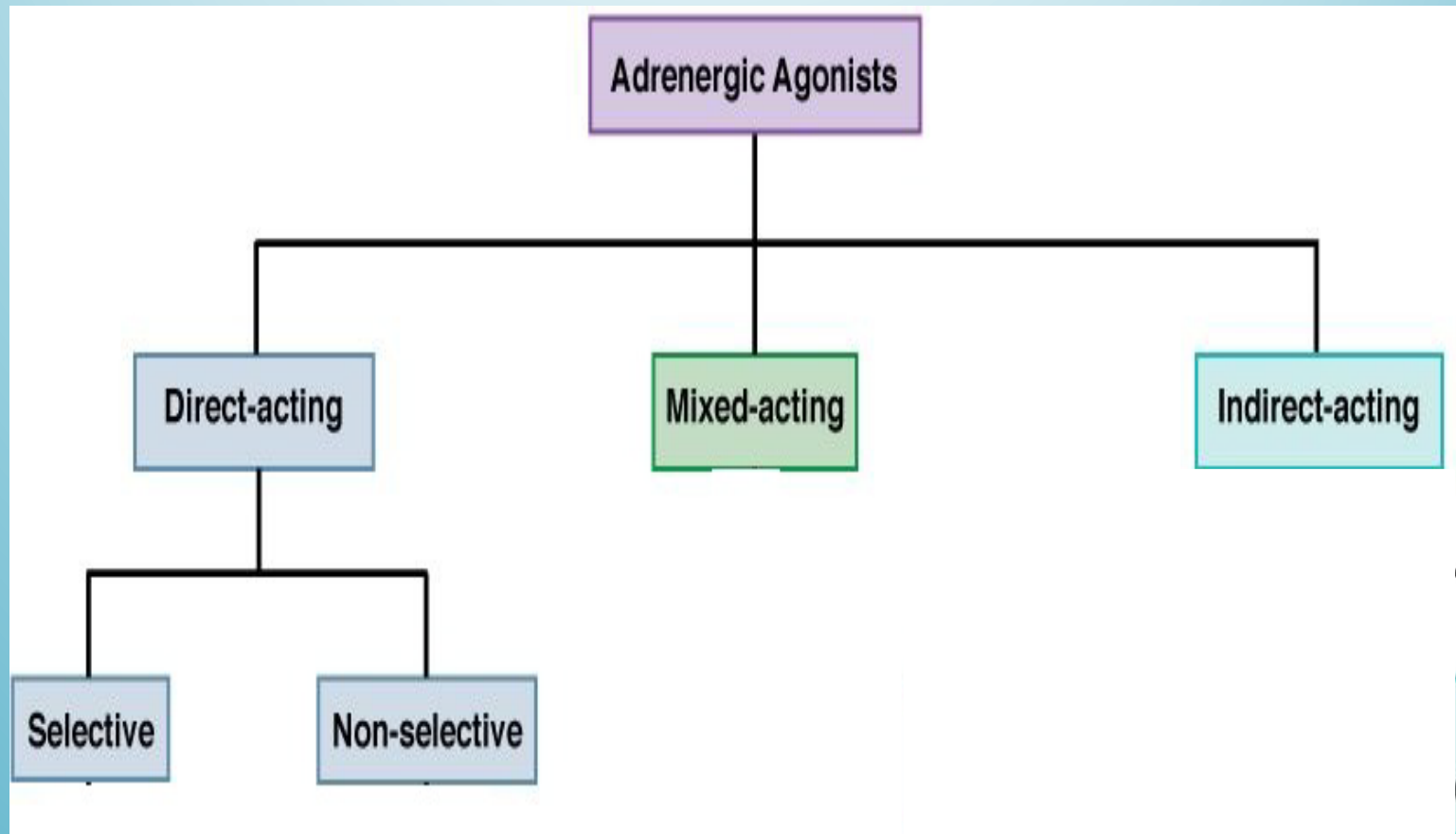
**A. Response to sympathetic activation**





|            |  |  |
|------------|--|--|
| $\alpha_1$ | Most vascular smooth muscle (innervated)   | Contraction  |
| $\alpha_2$ | Prostate<br>Postsynaptic CNS neurons<br>Adrenergic and cholinergic nerve terminals | Contraction<br>Probably multiple<br>Inhibits transmitter release |
| $\beta_1$  | Heart, juxtaglomerular cells   | Increases force and rate of contraction; increases renin release |
| $\beta_2$  | Respiratory, uterine, and vascular smooth muscle                                   | Promotes smooth muscle relaxation                                |
|            | Skeletal muscle  | Promotes potassium uptake  |
|            | Human liver  | Activates glycogenolysis   |
| $\beta_3$  | Fat cells  | Activates lipolysis  |
| $D_1$      | Smooth muscle  | Dilates renal blood vessels                                      |

# Classification of Sympathomimetics



# Adrenergic agonists



A. Direct acting Sympathomimetics.

B. Indirect acting Sympathomimetics.

C. Mixed acting Sympathomimetics.



**A. Direct acting Symapthomimetics.**

B. Indirect acting Symapthomimetics.

C. Mixed acting Symapthomimetics.

# Non-Selective adrenergic agonists

|                    | <i>Epinephrine</i>  | <i>Nor epinephrine</i>                      |
|--------------------|---|---|
| <b>Selectivity</b> | $\alpha_1 = \alpha_2$   |   |
|                    | $\beta_1 = \beta_2$   | $\beta_1 \gg \beta_2$                       |
| <b>Actions</b>     | + inotropic & chronotropic,<br>↑ renin release and<br>bronchodilation | Similar to EN but without<br>+ chronotropic |

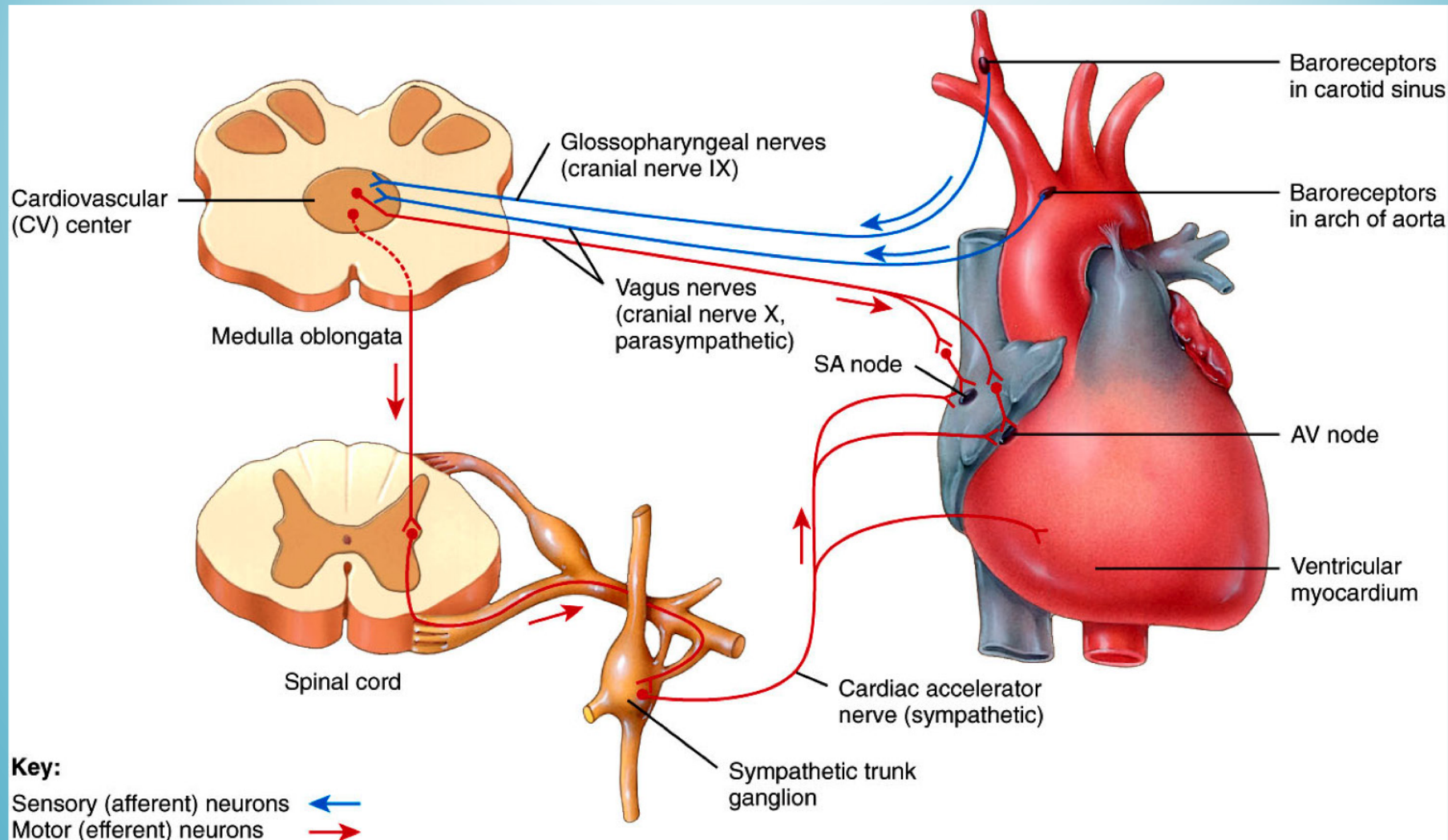
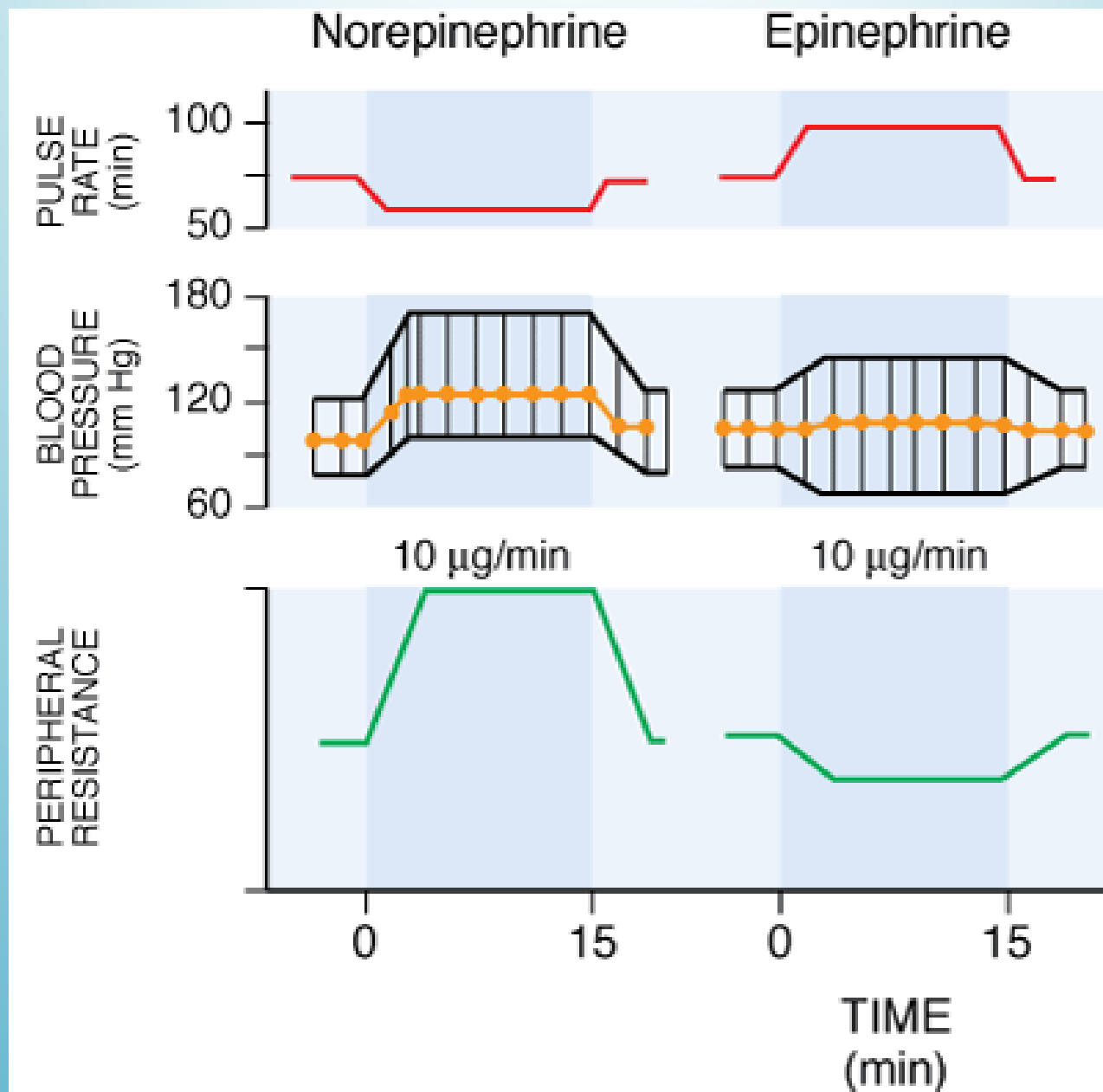


Figure 21.13 Tortora - PAP 12/e  
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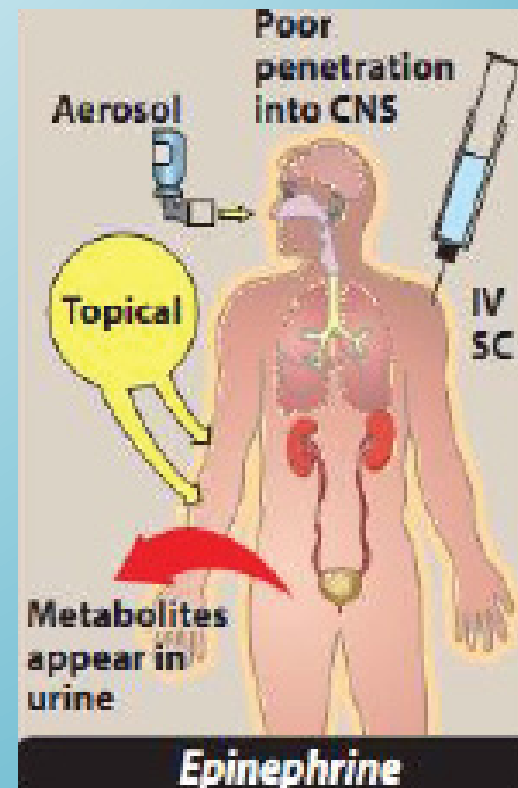


# Epinephrine / Nor-epinephrine

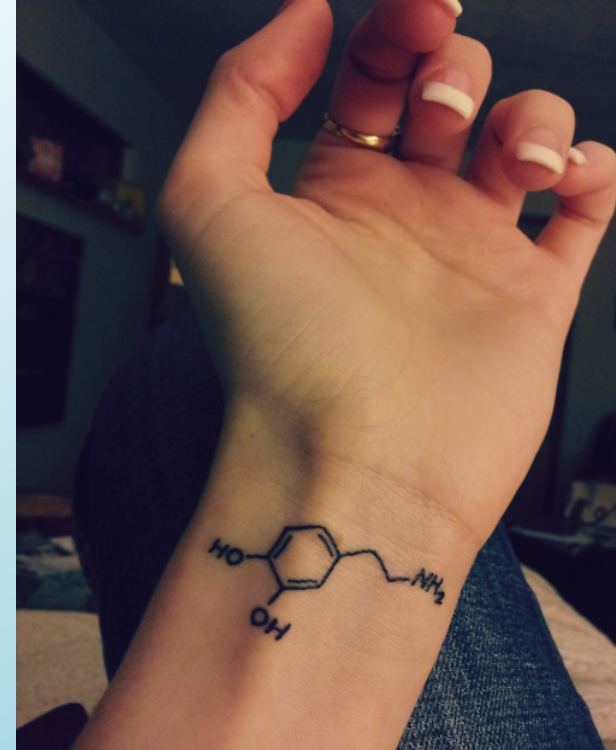
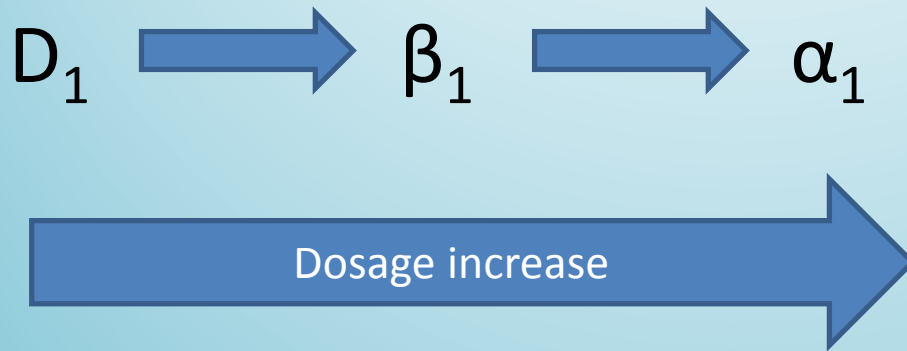
- Rapid onset , very short duration of action,  
Why?

## Adverse effects:

1. **CNS** : Anxiety , tremor & headache.
2. **CVS** : Arrhythmia & haemorrhage.
3. Hyperglycemia.



# Dopamine



- Fenoldopam is a selective  $D_1$  agonist used in treatment of ***severe hypertension***.

# $\alpha$ agonists

# $\alpha_1$ agonists

## **Phenylphrine**

*Used as mydriatic, decongestant and for management of hypotension.*

## **Midodrine , Methoxamine**

*Used for management of orthostatic hypotension.*

# $\alpha_2$ agonists

- ✓ **Clonidine, Methyldopa, Guanfacine and Guanabenz**  
*for management of HTN*
- ✓ **Moxonidine and Rilmenidine**  
*for management of HTN, but with fewer CNS side effects (less sedating).*
- ✓ **Dexmedetomidine**  
*for Sedation of initially intubated patients.*
- ✓ **Tizanidine**  
*used as central muscle relaxant.*



# $\alpha_1 / \alpha_2$ agonists

- **Xylometazoline, Oxmetazoline, Naphazoline**
- Used as Nasal decongestants.
- Large doses may cause hypotension ( $\alpha_2$ ).
- Prolonged use causes rebound congestion.

# $\beta$ agonists

# $\beta_1$ / $\beta_2$ agonists

|                               | <i>Isoproterenol<br/>(isoprenaline)</i> | <i>Dobutamine and<br/>Prenalterol</i> |
|-------------------------------|---|---------------------------------------|
| <b>Selectivity</b>            | $\beta_1 = \beta_2$                     | $\beta_1 > \beta_2$                   |
| <b>Reflex<br/>tachycardia</b> | High                                    | Less                                  |
| <b>Actions</b>                | + inotropic and chronotropic effects    |                                       |
| <b>Indications</b>            | CHF, Shock                              |                                       |

# $\beta_2$ agonists

- ❑ Short-acting: ***Ritodrine, Albuterol & Terbutaline.***
- ❑ Long-acting : ***Salmeterol & Formoterol.***
- ❑ Ultra-long acting: ***Indacaterol.***

- Indications :-

Asthma, Hyperkalemia.

# $\beta_3$ agonists

## **Mirabegron**

- relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder.
- Should not be used in uncontrolled HTN.



A. Direct acting Symapthomimetics.

**B. Indirect acting Symapthomimetics.**

C. Mixed acting Symapthomimetics.



Indirect acting  
Symapthomimetics

```
graph LR; A[Indirect acting Symapthomimetics] --- B[Amphetamine-like]; A --- C[Reuptake inhibitors];
```

Amphetamine-like

Reuptake inhibitors

# 1. Amphetamine-like

## **Amphetamine, Methamphetamine** **Methylphenidate, Modafinil and Pemoline**

- *↑ release of NE, DA by displacing stored catecholamines.*
- *Stimulant effect on mood/alertness, appetite suppressant.*
- *D-isomer of amphetamine is more potent, methamphetamine has higher ratio of central to peripheral actions than amphetamine.*

## 2. Reuptake inhibitors

### **Atomoxetine and Reboxetine**

- Selective inhibitors of NET.
- Little CVS S/E due to central clonidine-like effects.

### **Cocaine**

- Inhibits NET, SERT and DAT.
- Has a local anaesthetic effect.



A. Direct acting Symapthomimetics.

B. Indirect acting Symapthomimetics.

**C. Mixed acting Symapthomimetics.**

- **Ephedrine** & **Pseudoephedrine** (less potent) : ↑ NE release & directly activate  $\alpha$  and  $\beta$  receptors.

### *Actions:*

Similar to EN but much less potent.

### *Uses:*

Appetite suppressants, mild stimulants & nasal decongestants.

# Clinical Pharmacology

## Cardiovascular applications

- a. Acute hypotension, chronic orthostatic hypotension ( $\alpha_1$  agonists)
- b. Induction of local vasoconstriction ( $\alpha_1$  agonists).
- c. Shock (+ inotropic drugs).
- d. Heart block / Cardiac arrest ( $\beta_1$  agonists).



## **Pulmonary applications**

Bronchial asthma , COPD

$\beta_2$  agonists

## **Ophthalmic applications**

- Mydriatic, decongestant
- Glaucoma

$\alpha_1$  agonists

$\alpha_2$  agonists

## **Genitourinary applications**

- Suppress preterm labor
- Stress incontinence

$\beta_2$  agonists

Mixed-acting

## **CNS applications**

- Amphetamines, Methylphenidate, Atomoxetine , Clonidine & Guanfacine are used in treatment of ADHD.
- Modafinil is used in the treatment of narcolepsy.

## **Other applications**

- Clonidine is also used in treatment of hypertension, diarrhoea in diabetics and can ↓ craving for alcohol, narcotics & cigarettes.

# References

- Lippincott's Illustrated Reviews: Pharmacology , 6<sup>th</sup> edition.
- Basic & Clinical Pharmacology , Bertram G. Katzung 12<sup>th</sup> edition .
- Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12<sup>th</sup> ed. .