بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

Sympathomimetics (adrenergic drugs)

These drugs activate the **adrenoceptors** to mimic the effects of endogenous catecholamines such as epinephrine & norepinephrine.

Sympathetic agonists
Adrenoceptor agonists
Adrenoceptor activating drugs
By
DR. M. Sarwar

Adrenergic receptors;

- **Alpha receptors;**

  α_1, α_2

- **Beta receptors;**

  β_1, β_2, β_3

- **Dopaminergic receptors;**
  (a subclass of adrenoceptors)

  D_1, D_2, D_3, D_4, D_5

All are G-protein coupled.

- α_1 ------- **Gq**
- α_2 ------- **Gi**
- β ------- **Gs**
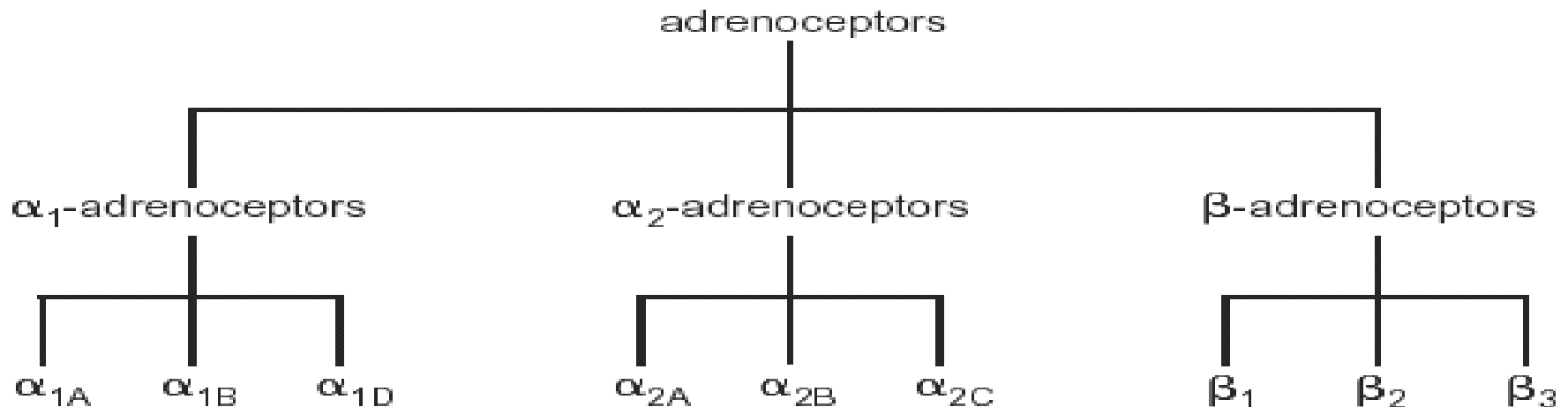
Figure. **Classification of adrenoceptors.**

Alpha receptors; α₁, α₂

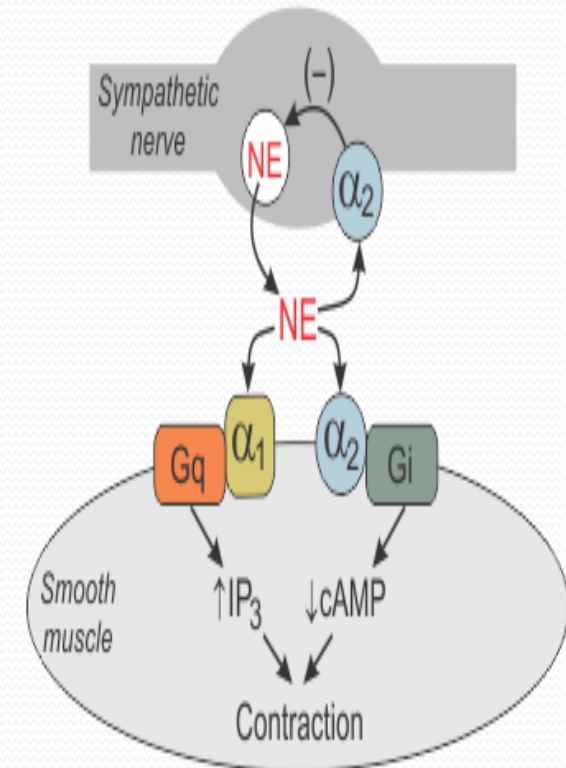|			
α₁	• **Blood vessels.** • **Pupillary dilator muscle.** • **Prostate.** (Urethral sphincter)	**Vasoconstriction.** (↑peripheral resistance ↑blood pressure) **Mydriasis.** **Contraction.** (Increased closure of internal sphincter of bladder)	• α₁ ------ **Gq** • α₂ ------**Gi**
α₂	• **Presynaptic terminals.** • Some Blood vessels. • **Pancreatic β cells.**	**Inhibition of NA release.** Vasoconstriction. **Inhibition of Insulin release.**	

α₂ receptors----Regulatory Receptors;

Alpha 2 receptors
(presynaptic actions)

Autonomic neuromodulation

Pancreatic ß cell

Inhibition of **norepinephrine** release (Inhibitory autoreceptors)

Inhibition of **acetylcholine** release (Inhibitory heteroreceptors)

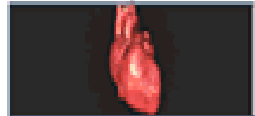Inhibition of **insulin release**
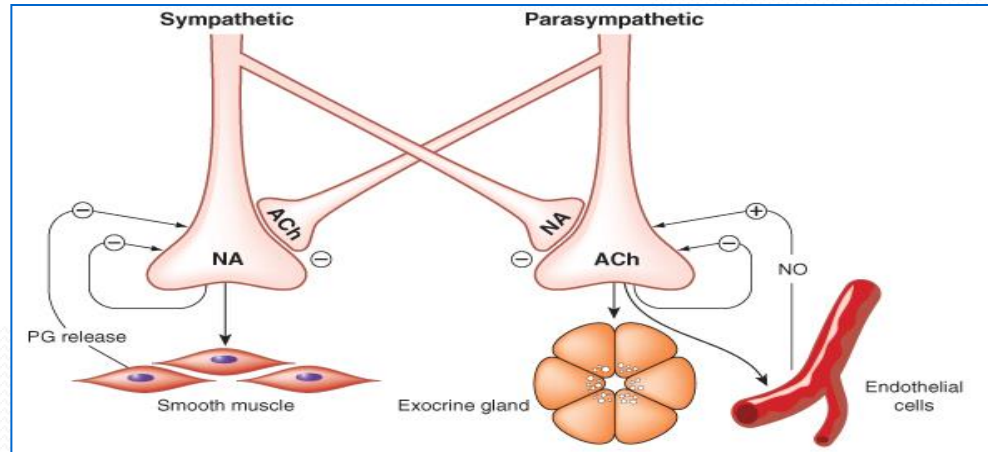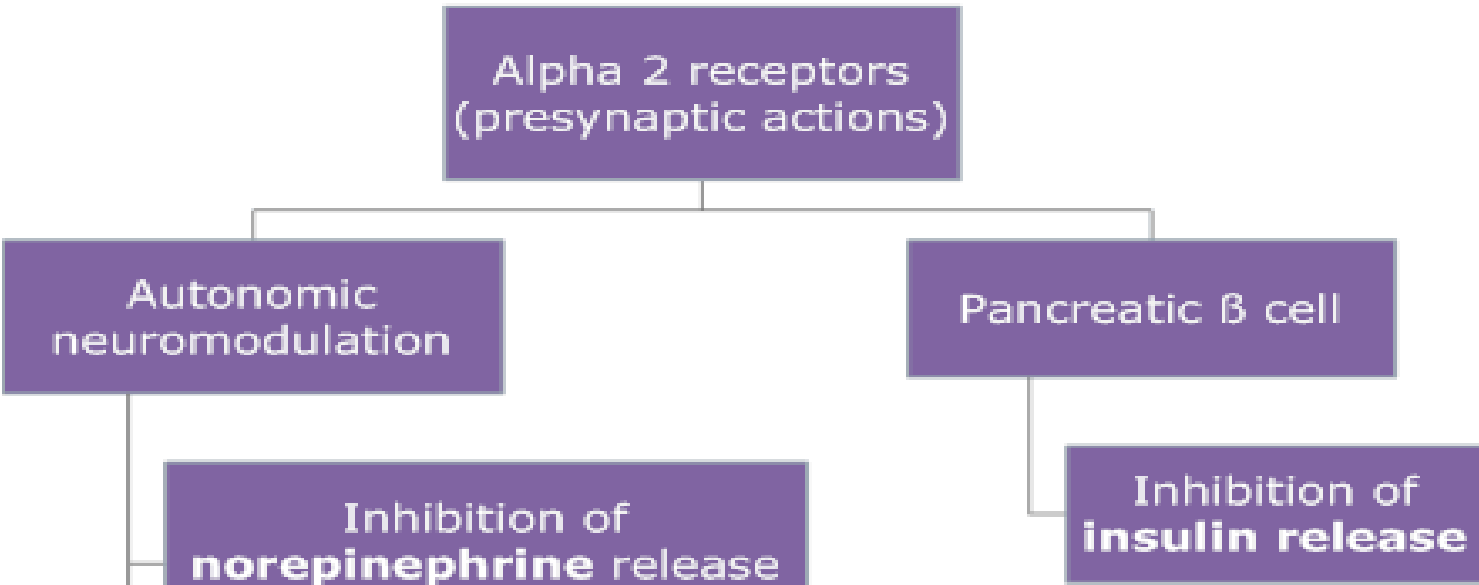
Presynaptic regulation of transmitter release from noradrenergic and cholinergic nerve terminal

β – Adrenoceptors; (β ------Gs)

- **β1**
  - **Heart;**   **Stimulate**
    (SA node, AV node, cardiac muscles)
  - **Juxtaglomerular cells;**   **Renin release**
- **β2**
  - **Respiratory smooth muscles**   **Relax**
  - **Uterine smooth muscle**   **Relax**
  - **Vascular smooth muscle**   **Relax**
  - **Skeletal muscle**   **K$^+$ uptake**
  - **Pancreatic β & α cells.**   **Increased**
                                                    insulin & glucagon secretion
- **β3**
  - **fat**   **Stimulate lipolysis**

β1 adrenoceptors;
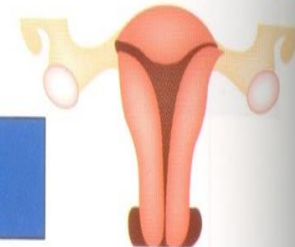
Characteristic responses;

ADRENOCEPTORS

α_1
- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

α_2
- Inhibition of *norepinephrine* release
- Inhibition of insulin release

β_1
- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

β_2
- Vasodilation
- Slightly decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis
- Increased release of glucagon
- Relaxed uterine smooth muscle

Dopamine receptors;

D₁. Renal blood vessels ------ Vasodilation
---- mechanism of action;

dopamine >> Epi = NE
or SKB-38393

7-TMD

Beta receptor

β
α

GDP

GTP   GDP

α

GTP

Adenylyl cyclase

+

ATP   cAMP

D1-dopamine receptors
coupled to Gs-protein
-> increased cAMP

Enzyme

ATP

ADP

Enzyme-PO₄

Biologic effect

+   2C

R₂C₂ protein kinase

+

2R

Kidney: Vasodilation.
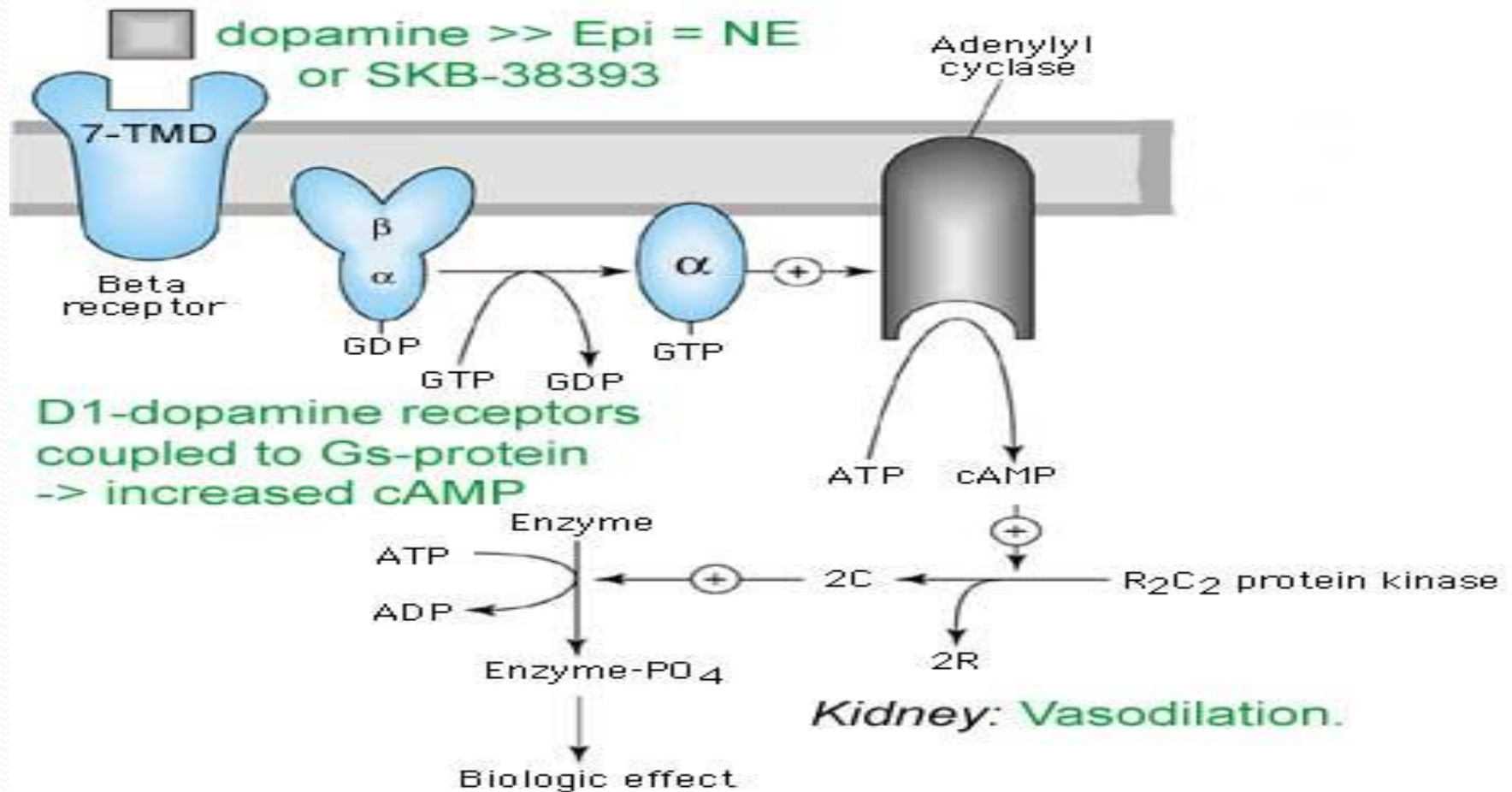
Receptor	Location	G Protein	Second Messenger	Major Functions
Alpha$_1$ (α_1)	Effector tissues: smooth muscle, glands	G_q	↑IP$_3$, DAG	Ca^{2+}, causes contraction, secretion
Alpha$_2$ (α_2)	Nerve endings, some smooth muscle	G_i	↓cAMP	Transmitter release, causes contraction
Beta$_1$ (β_1)	Cardiac muscle, juxtaglomerular apparatus	G_s	↑cAMP	Heart rate, force; renin release
Beta$_2$ (β_2)	Smooth muscle, liver, heart	G_s	↑cAMP	Relax smooth muscle; glycogenolysis; heart rate, force
Beta$_3$ (β_3)	Adipose cells	G_s	↑cAMP	Lipolysis
Dopamine$_1$ (D_1)	Smooth muscle	G_s	↑cAMP	Relax renal vascular smooth muscle

Classification of Adrenergic Drugs;

- May be classified according to
    - ❖**Receptors** on which drugs act.
    - ❖**Mode of action;**
        - ➢ **Direct, indirect, mixed.**
    - ❖**Chemical structure.**
    - ❖**Therapeutic uses.**

❖**Classification according to receptor selectivity;**

- A drug may **preferentially binds** to one subgroup of receptors at **concentration** too low to interact with another subgroup.
- **Selectively** is **not** usually **absolute**.
- NA preferentially activates β_1 receptors as compared to β_2 receptors.

Alpha$_1$ Agonists;

- Phenylephrine
- Methoxamine (has some β blocking effect also)
- Xylometazoline
- Oxymetazoline
- Naphazoline

Alpha$_2$ Agonists;

- **Clonidine**,
- **α methyldopa** (alpha methyl noradrenaline).
  - ❖ They inhibit central sympathetic outflow and act as anti hypertensive agents.

β agonists;

- **β1 selective agonists;**
  - Dobutamine
- **β2 selective agonists;**
  - Salbutamol,
  - Terbutaline,
  - Procaterol,
  - Rimiterol,
  - Formeterol
  - Fenoterol,
  - Pirbuterol,
  - Ritodrine.

Acting on both β1 and β2 receptors;
  - Isoprenaline,
  - Orciprenaline.

Acting on both α and β receptors;

- Adrenaline,
- Ephedrine,
- Amphetamine,
- Dexamphetamine,
- Methyl amphetamine,
- Hydroxyamphetamine,
- Metaraminol.

Dopaminergic agonists;

- **Dopamine Selectivity;**
  - **Low dose;**
    - **Dopaminergic receptors (renal &** splanchnic blood vessels) D_1-------- Vasodilatation.
  - **Moderate dose;**
    - **β_1 agonist activity** --- increase in contraction and cardiac output.
  - **High dose;**
    - **Act on α_1 receptors** in BV causing vasoconstriction and increase total peripheral resistance causing increase in systolic and diastolic blood pressure.

Relative receptor selectivity of adrenergic drugs;

Alpha agonists

Phenylephrine, methoxamine
$\alpha_1 > \alpha_2 >>>>> \beta$

Clonidine, methylnorepinephrine
$\alpha_2 > \alpha_1 >>>>> \beta$

Mixed alpha and beta agonists

Norepinephrine
$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$

Epinephrine
$\alpha_1 = \alpha_2; \beta_1 = \beta_2$

Beta agonists

Dobutamine[1]
$\beta_1 > \beta_2 >>>>> \alpha$

Isoproterenol
$\beta_1 = \beta_2 >>>>> \alpha$

Terbutaline, metaproterenol, albuterol, ritodrine
$\beta_2 >> \beta_1 >>>> \alpha$

Dopamine agonists

Dopamine
$D_1 = D_2 >> \beta >> \alpha$

Fenoldopam
$D_1 >> D_2$