

By

Dr/Yasmeen Mohammed Ismail

Associate professor of pharmacology

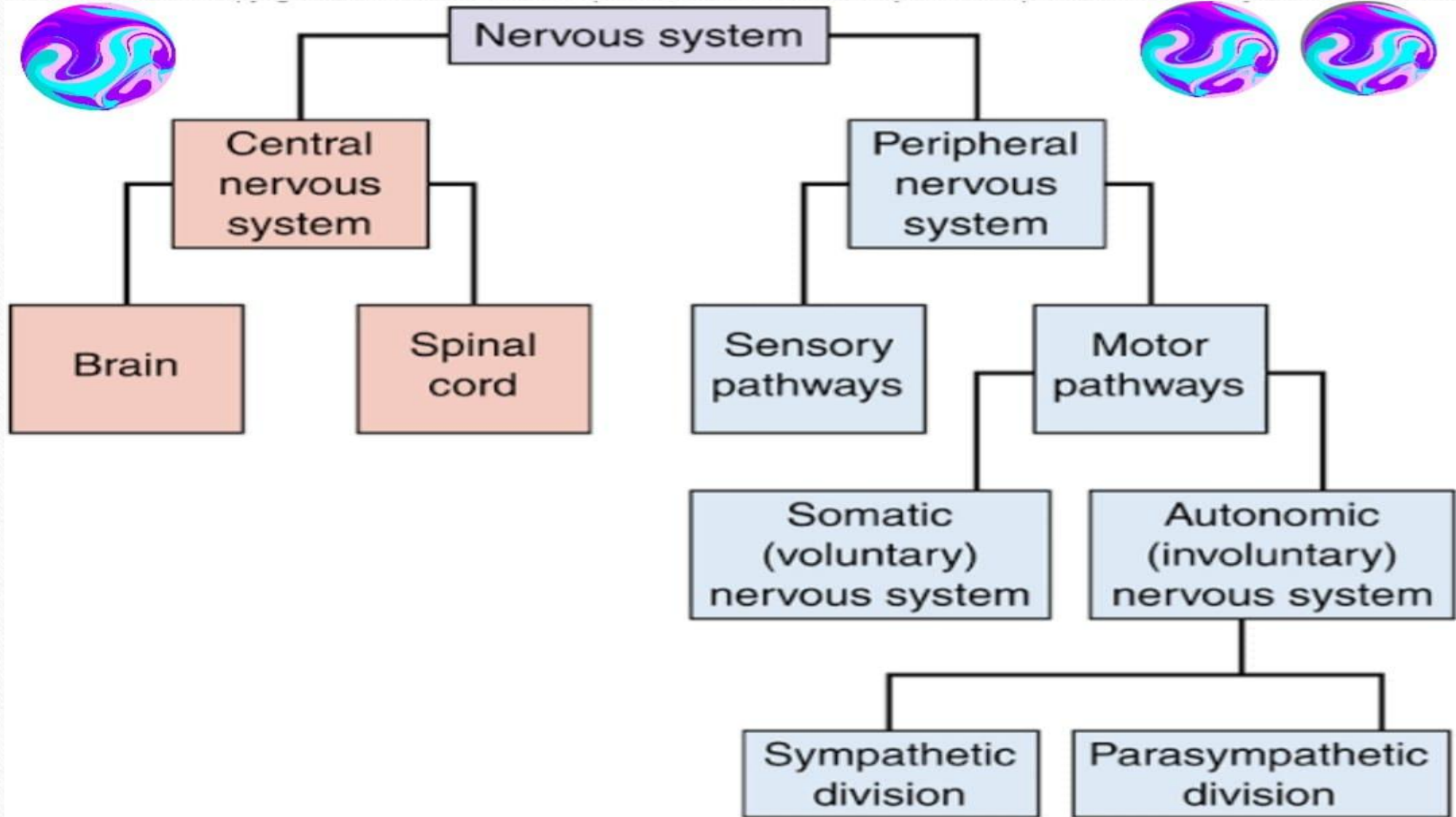
faculty of medicine

Hashemite university

*Adrenergic
Pharmacology*

(1)

sympathomimetics



Autonomic nervous system

It regulates involuntary functions of the body which •
are:

- 1-Cardiovascular system(CVS)
- 2-Smooth muscles fibres(SMF)
- 3- Exocrine glandsAutonomic

Autonomic nervous system includes :

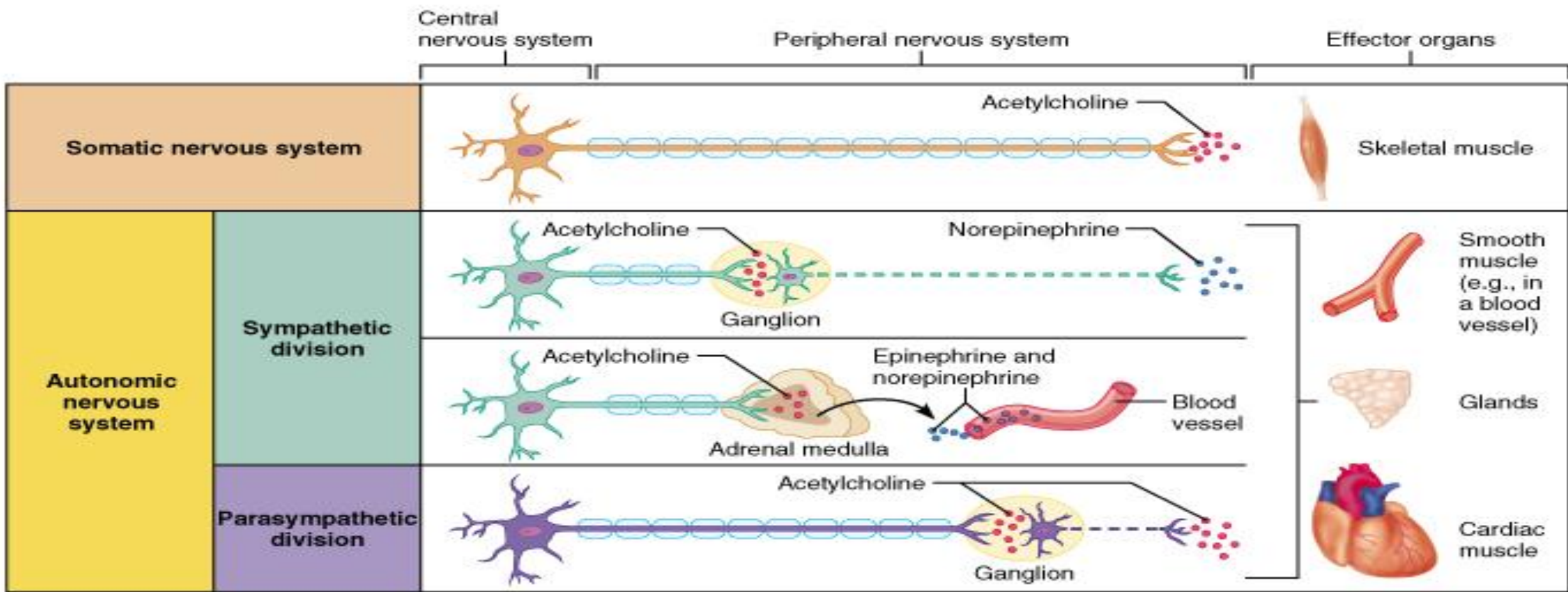
-Sympathetic - Parasympathetic

Sympathetic vs. Parasympathetic Structural Differences

Symp.

Parasymp.

	<u>Symp.</u>	<u>Parasymp.</u>
<i>Point of CNS Origin</i>	T1 → L2 (thoracolumbar)	Brainstem, S2 → S4 (craniosacral)
<i>Site of Peripheral Ganglia</i>	Paravertebral – in sympathetic chain	On or near target tissue
<i>Length of preganglionic fiber</i>	Short	Long
<i>Length of postganglionic fiber</i>	Long	Short



Key:






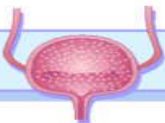


- = Preganglionic axons (sympathetic)
- = Postganglionic axons (sympathetic)
- = Myelination
- = Preganglionic axons (parasympathetic)
- = Postganglionic axons (parasympathetic)

	Sympathatic action	Parasympathatic action
<u>CVS</u> Heart	Increase all cardiac properities	Decrease all cardiac properities except atrial conduction
Blood vessels	VC of skin and mm VD of skeletal and coronary blood vessels	Non innervated
Blood pressure	Hypertension	Hypotension

SMF

Eye	Active mydriasis	Miosis
Bronchi	Bronchodilatation	Bronchocnstriction
GIT	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Urinary tract	Inhibit motility of wall Contract sphincter	Contract wall Relax sphincter
Sex organ	Ejaculation in males Relax uterine wall in female	Erection in male
<u>Exocrine glands</u>		
Salivary glands	Thick viscid secretion	Profuse watery secretion No effect
Sweet glands	Increase	

Figure 20-2
Sympathetic and Parasympathetic Effects on Body Tissues

BODY TISSUE/ORGAN		SYMPATHETIC RESPONSE*	PARASYMPATHETIC RESPONSE*
Eye		Dilates pupils	Constricts pupils
Lungs		Dilates bronchioles	Constricts bronchioles and increases secretions
Heart		Increases heart rate	Decreases heart rate
Blood vessels		Constricts blood vessels	Dilates blood vessels
Gastrointestinal		Relaxes smooth muscles of gastrointestinal tract	Increases peristalsis
Bladder		Relaxes bladder muscle	Constricts bladder
Uterus		Relaxes uterine muscle	
Salivary gland			Increases salivation

*The sympathetic and parasympathetic nervous systems have opposite responses on body tissues and organs.

SYMPATHATIC

- ****Chemical transmitter**

- ****Types of adrenergic receptors: $\alpha - \beta$**

- ****Mechanism of actions of adrenergic receptors:**

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- **They are G protein coupled receptors**

- **1-Alpha 1: Gq proteins: stimulate**

- **Phospholipase C \rightarrow \uparrow IP3 and DAG \rightarrow \uparrow intracellular ca**

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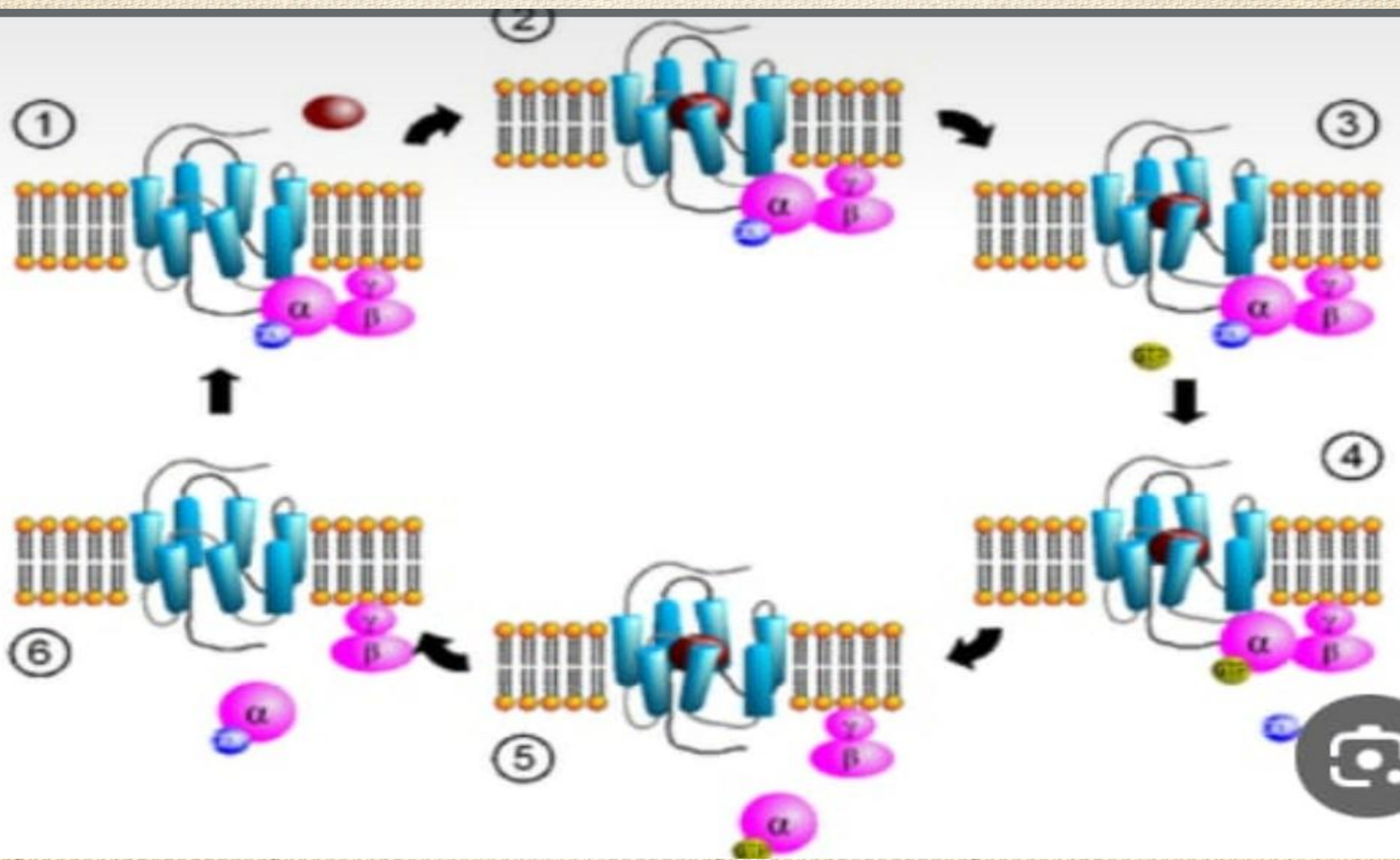
- **2-Alpha 2: Gi proteins: decrease adenylyl cyclase \rightarrow \downarrow CAMP**

- **3-Beta receptors: Gs proteins: stimulate adenylyl cyclase \rightarrow \uparrow CAMP**

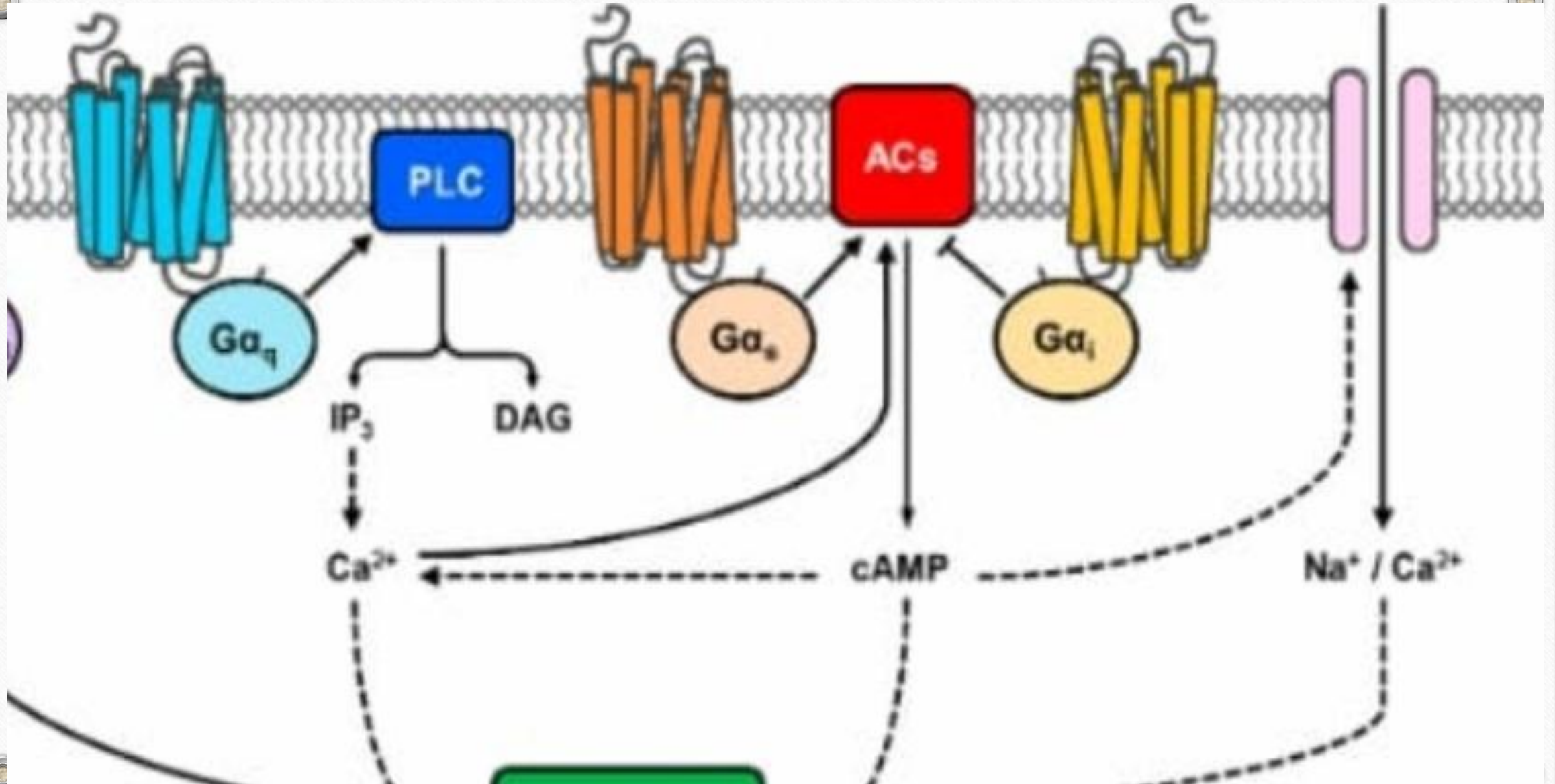
Molecular Mechanism of Action of Sympathomimetics

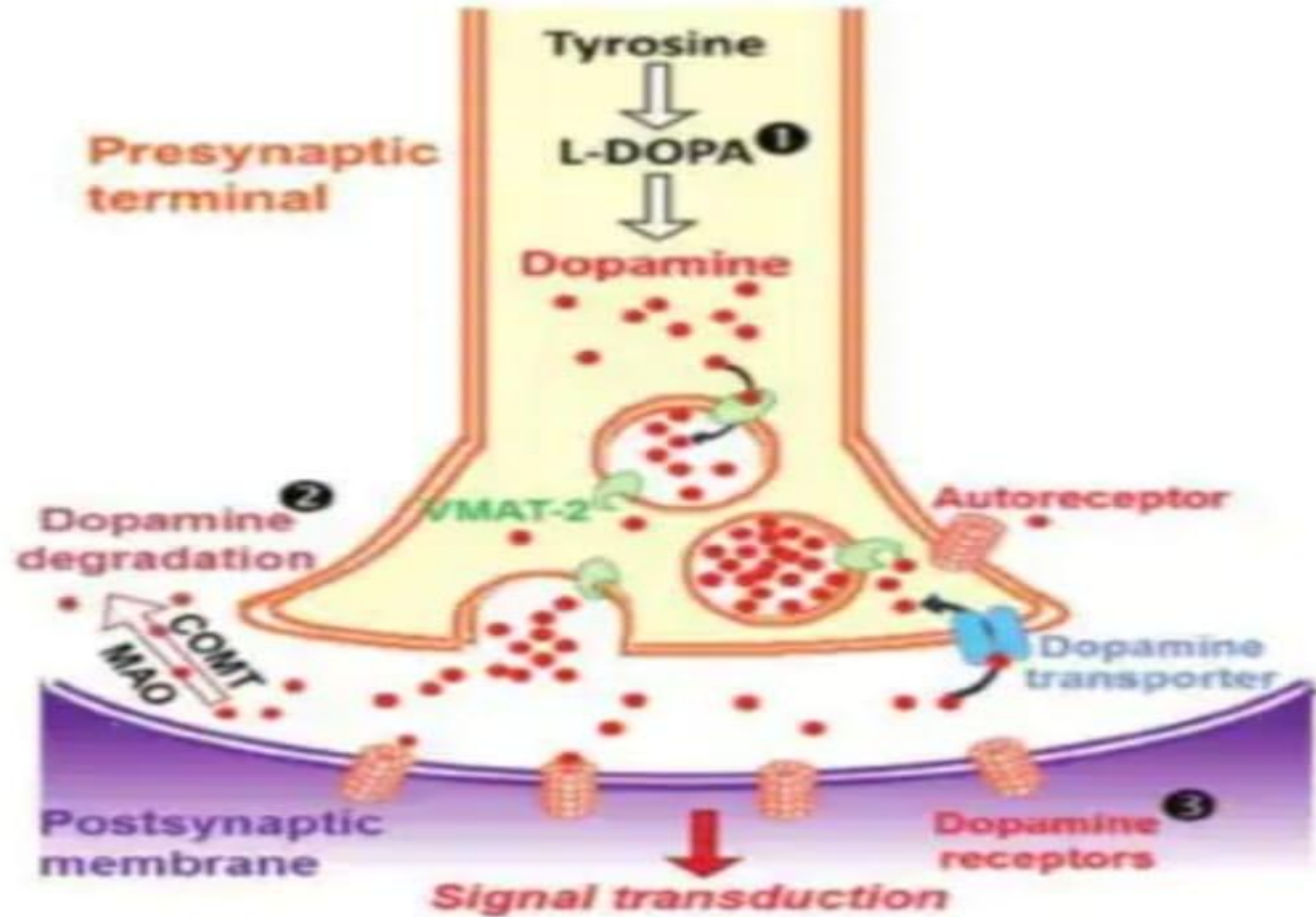
Table 6–3. Characteristics of some important adrenoceptors in the ANS.

Receptor	Location	G Protein	Second Messenger	Major Functions
α_1	Effector tissues: smooth muscle, glands	G_q	\uparrow IP_3 , DAG	\uparrow Ca^{2+} , causes contraction, secretion
α_2	Nerve endings, some smooth muscle	G_i	\downarrow cAMP	\downarrow Transmitter release, causes contraction
β_1	Cardiac muscle, juxtaglomerular apparatus	G_s	\uparrow cAMP	\uparrow Heart rate, \uparrow force; \uparrow renin release
β_2	Smooth muscle, cardiac muscle	G_s	\uparrow cAMP	Relax smooth muscle; \uparrow glycogenolysis; \uparrow heart rate, force
β_3	Adipose cells	G_s	\uparrow cAMP	\uparrow Lipolysis
D_1	Smooth muscle	G_s	\uparrow cAMP	Relax renal vascular smooth muscle



Molecular Mechanism of Action of Sympathomimetics





$\alpha 1$ •

- **1-CVS: V.C of skin and mm membrane blood vessels**
 - **2-SMF: - Eye : Iris ms (dilator pupillae → mydriasis)**
 - **3-Salivary glands**
-

$\alpha 2$ •

(inhibitory) •

- **1-CNS: inhibit sympathetic centres → ↓ sympathetic outflow**
- **2-Presynaptic → It decrease NA release**

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Beta 1 •

- **1-CVS: Heart: Increase all cardiac properties**
(~~Contractility-Conductivity-Excitability-Heart rate~~) and
C.O.P-O₂ consumption
- **2-SMF: - Eye : Cilary epithelium → ↑ aqueous secretion**
(↑IOP)
- **3-Other actions:**
 - **-Kidney: Renin secretion •**
 - **-CNS: ↑ sympathetic outflow**

Beta 2 •

- **1-CVS: VD of skeletal and coronary blood vessels**
- **2-SMF: - Eye: Ciliary epithelium → ↑ aqueous secretion (↑ IOP)**
- **-Bronchi: relaxation**

- **-GIT and urinary wall : relaxation**
- **-Uterus: relaxation**
- **3-Other actions:**
- **-Liver: Glycogenolysis → ↑ glucose**
- **-Skeletal muscles: - Muscles tremors •**
- **-↑uptake of K by skeletal muscles → Hypokalemia •**

Beta 3 •

- **Fat cells : ↑ lipolysis**

- ▶ Diameter of blood vessels
- ▶ Vasoconstriction → increased afterload ≡ high TPR
- ▶ Vasodilation → decreased afterload ≡ low TPR



Normal cross-section

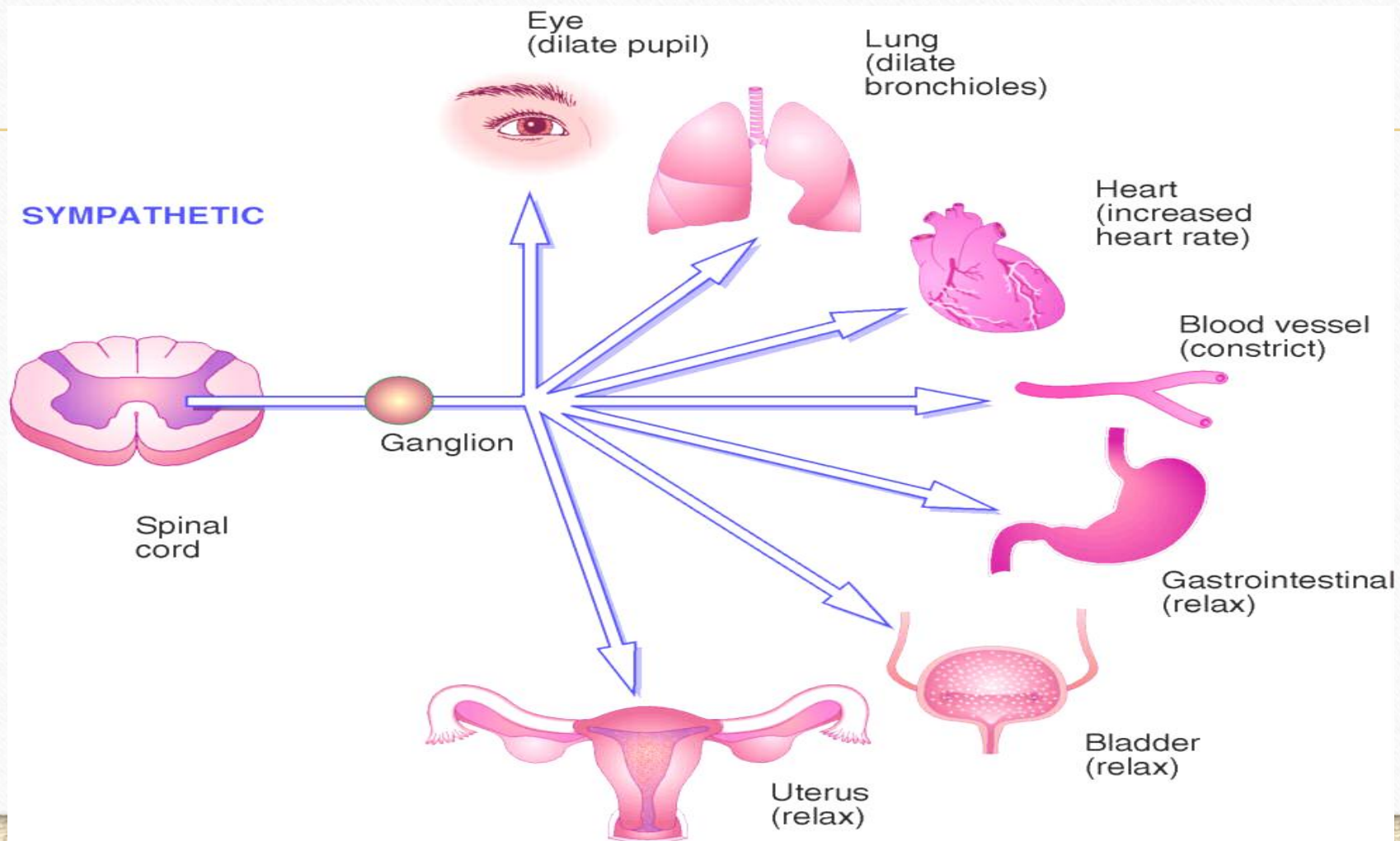


Vasoconstriction



Vasodilation

SYMPATHETIC RESPONSES



- **Sympathomimetics**

- **Drugs that produce actions similar to sympathetic nerve stimulation.**
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- **Classifications:**

- ***1-According to Chemistry:***

- ***2. According to Mechanism of Action:***

Catecholamines

- Contain catechol nucleus
- Not absorbed orally
- Rapid onset, short duration
- can not pass BBB
- Metabolized by MAO and COMT.
- Adrenaline, noradrenaline
Dopamine, Isoprenaline,
Dobutamine.

Non-catecholamine

- Don't contain catechol nucleus
- Well absorbed orally
- Slow onset, long duration
- can pass BBB
- Not metabolized by MAO or COMT
- Ephedrine, Amphetamine

Direct	Indirect	Dual
<p>-Direct stimulation of the receptor include:</p>	<p>Release Nor-adrenaline from vesicles</p>	<p>- Dual mechanism</p>
<p>Effect increased after Sympathectomy (supersensitivity)</p> <p>- No Tachyphylaxis</p>	<p>Absent</p> <p>Present</p>	<p>Present</p> <p>Present</p>
<p>Adrenaline,</p> <p>Noradrenaline</p> <p>Isoprenaline</p> <p>Dopamine</p> <p>Dobutamine</p>	<p>Amphe tamine</p> <p>Tyramine</p>	<p>Ephedrine</p>

Catecholamine

**Adrenaline - Noradrenaline -
Dopamine - Isoprenaline, Dobutamine.**

Adrenaline=Epinephrine (α +B)

Routes of administration:

local on eye- inhalation- intracardiac- SC- not oral

• Pharmacological actions:

• Systemic effects

- local effects:

- Systemic effects:

- - Cardiovascular system:

- -heart: adrenaline increase all properties of the cardiac muscle through action on (B 1).

- Increase (↑) heart rate - (↑) contractility- (↑) conductivity

- (↑) excitability and automaticity of the heart - (↑) cardiac output (C.O.P.) and cardiac work

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- -Blood vessels: VC of blood vessels of skin, mucous membrane ($\alpha 1$)

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- VD of coronary and skeletal blood vessels (B2)

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- - Blood pressure (BP):

- -adrenaline increase C.O.P, so increase systolic BP with slight variation in diastolic BP

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- **2- Eye:**

- **A- pupil size: mydriasis ($\alpha 1$) and decongestion**

- **B- intraocular pressure (IOP) : decrease IOP (in open angle glaucoma)**

- **3-Respiratory system:**

- **Bronchodilation :B2**

- **Decongestion due to $\alpha 1$ stimulation of mucous membrane blood vessels**

- **4-GIT**

- **Relax wall (B2) - Contraction of sphincters ($\alpha 1$)**

- **5-Urinary**

- **Relax wall (B2)- Contraction of sphincters ($\alpha 1$)**

- **6-Sex organs**

- **Males : ejaculation ($\alpha 1$)**

- **Females: relaxation of pregnant human uterus (B2).**

- **7-Other actions:**

- **1-Kidney: Renin secretion \uparrow (B1)**
- **2-Liver: Glycogenolysis \rightarrow \uparrow glucose (B2)**
- **3-Sk. ms: -Muscles tremor(B2)**

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- **- \uparrow uptake of K by sk.ms (B2)**
 - **- Facilitate NM(neuromuscular) Transmission (α 1)**

4-Fat cells: Lipolysis(B3) •

• **-CNS: affect sympathetic flow** •

- **8- antiallergic action:**

- **Adrenaline is the physiological antagonist of histamine.**

- **- local effects:**

- **1- Vasoconstriction (VC) of cutaneous blood vessels ($\alpha 1$) :used to prolong action of local anesthetics**
- **2- VC of mucous membrane blood vessels of the nose ($\alpha 1$) : used as nasal pack for hemostasis in epistaxis**
- **3- VC of conjunctival blood vessels ($\alpha 1$)**
- **4- VC of mucous membrane blood vessels of the bronchi ($\alpha 1$) and bronchodilator (B2) :inhalation in acute bronchial asthma**

- **Therapeutic use:**

- **A- local uses:**

- **1- With local anaesthetics to prolong its effect.**
- **2- local hemostatic in epistaxis and bleeding surfaces**
- **3- Decongestion of m.m of nose and eye**
- **4- acute bronchial asthma :inhalation**
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- **B- systemic uses:**

- **1-Cardiac resuscitation: intracardiac .**
- **2-Acute attack of bronchial asthma: SC .**
- **3-Contraction ring during labour to relax the uterus**
- **4- Allergic reactions e.g. anaphylactic shock.**
- **5- Hypoglycemic coma (SC)**





Constriction ring

Side effects

Tachycardia, palpitation arrhythmia.

Hypertension and cerebral haemorrhage

If used with local anaesthesia in region of end arteries (Finger, toe, penis) → gangrene.

If used with general anaesthesia → ventricular fibrillation

Contraindications

Arrhythmia

Hypertension

with local anaesthesia in region of end arteries (Finger, toe, penis)

with general anaesthesia

- Noradrenaline (NA) = Norepinephrine

- (α +weak B1+No β 2)

- Therapeutic uses:

- In hypotensive states to elevate BP.

Isoprenaline (Beta only)

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- Therapeutic uses:
- **1-Heart block**
- **2-Bronchial asthma**

- **Dopamine**

- **(Dopaminergic receptors+ β_1 + α)**

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- **Therapeutic uses:**

- 1-Different types of shock (Cardiogenic, hemorrhagic & Septic shock) due to: * VD of renal blood vessels \rightarrow \uparrow renal blood flow

- * increase of C.O.P and systolic blood pressure.

- 2- Heart failure, hypotension

-

- **Dobutamine**

- **(Selective β_1 + weak α)**

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- **Therapeutic uses:**

- **1-Shock due to: increase of C.O.P and systolic blood pressure.**

- **2- Heart failure, hypotension**

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Non Catecholamines

CNS stimulant: as Ephedrine - Amphetamine

Anorexigenics: as Fenfluramine- Phenmetrazine

- ***Vasopressors*** as Methoxamine – Midodrine - Metraminol-
- **Phenyl ephrine** (weaker than NA)

Nasal decongestant **Old group:** as Phenylephrine – Pseudoephedrine

Recent group:as Naphazoline – Xylometazoline

Vasodilators and uterine relaxants as Isoxsuprine- Ritodrine

Bronchodilators as Salbutamol- Terbutaline- Salmeterol

Thanks
