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Drugs acting on PNS

**DRUGS AFFECTING THE SYMPATHETIC
NERVOUS SYSTEM**

adrenomimetics, dopaminomimetics

**(Drugs Affecting Adrenergic Synapses,
Adrenergic Substances)**

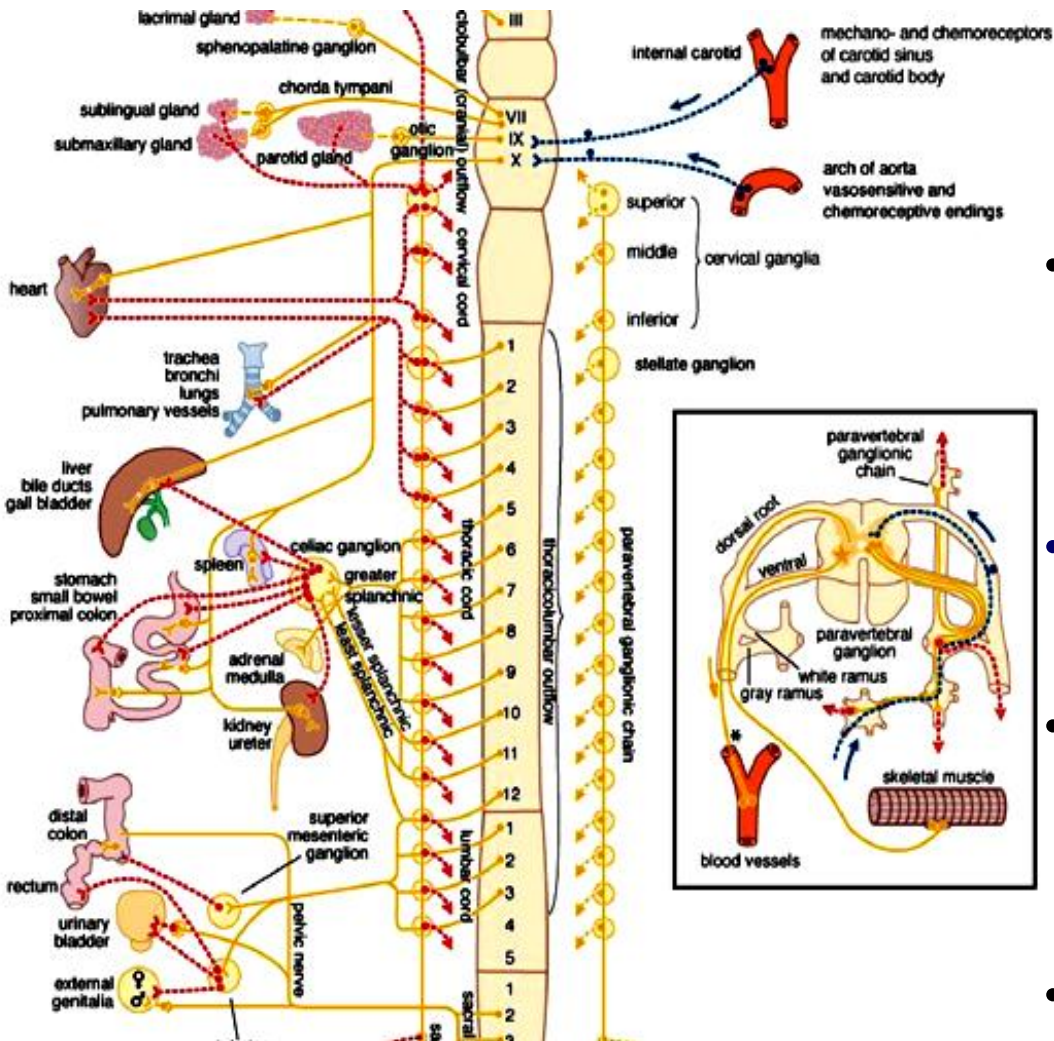
- The cell bodies of the sympathetic preganglionic neurons lie in the lateral horn of the grey matter of the thoracic and lumbar segments of the spinal cord

- Fibres leave the spinal cord in the spinal nerves as the thoracolumbar sympathetic outflow.

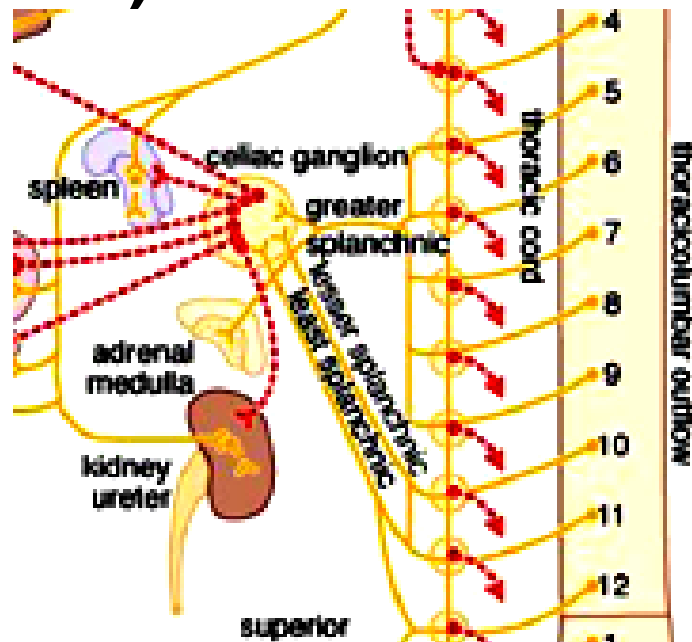
- The preganglionic fibres are short

- They synapse in the paravertebral chains of sympathetic ganglia, lying on either side of the spinal column.

- These ganglia contain the cell bodies of the postganglionic sympathetic neurons, the axons of which rejoin the spinal nerve.



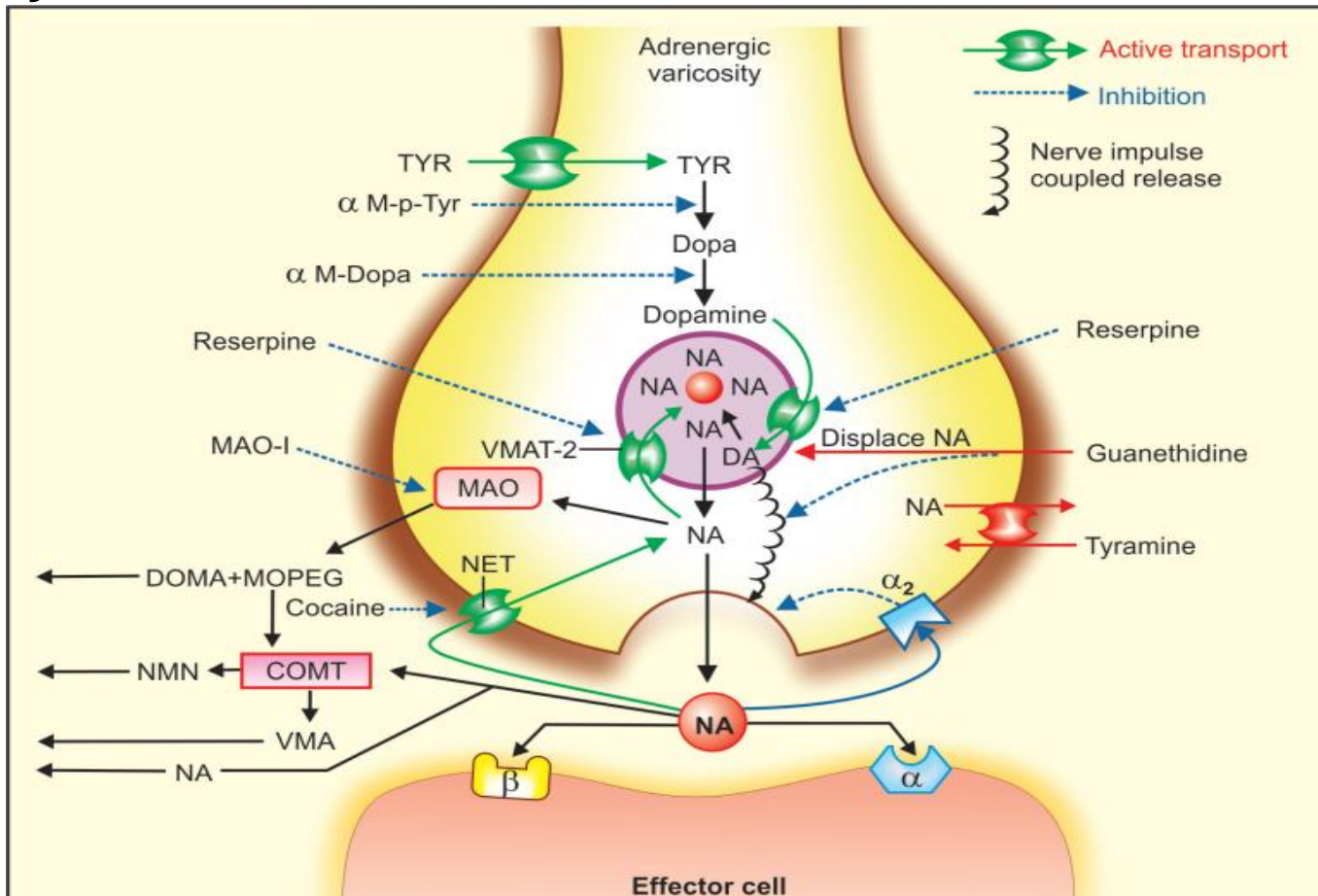
- The **postganglionic fibres** are long
- The catecholamine-secreting cells of the **adrenal medulla** are innervated by **preganglionic fibres**, and are, in effect, modified postganglionic sympathetic neurons (the only exception to the two-neuron arrangement in ANS).



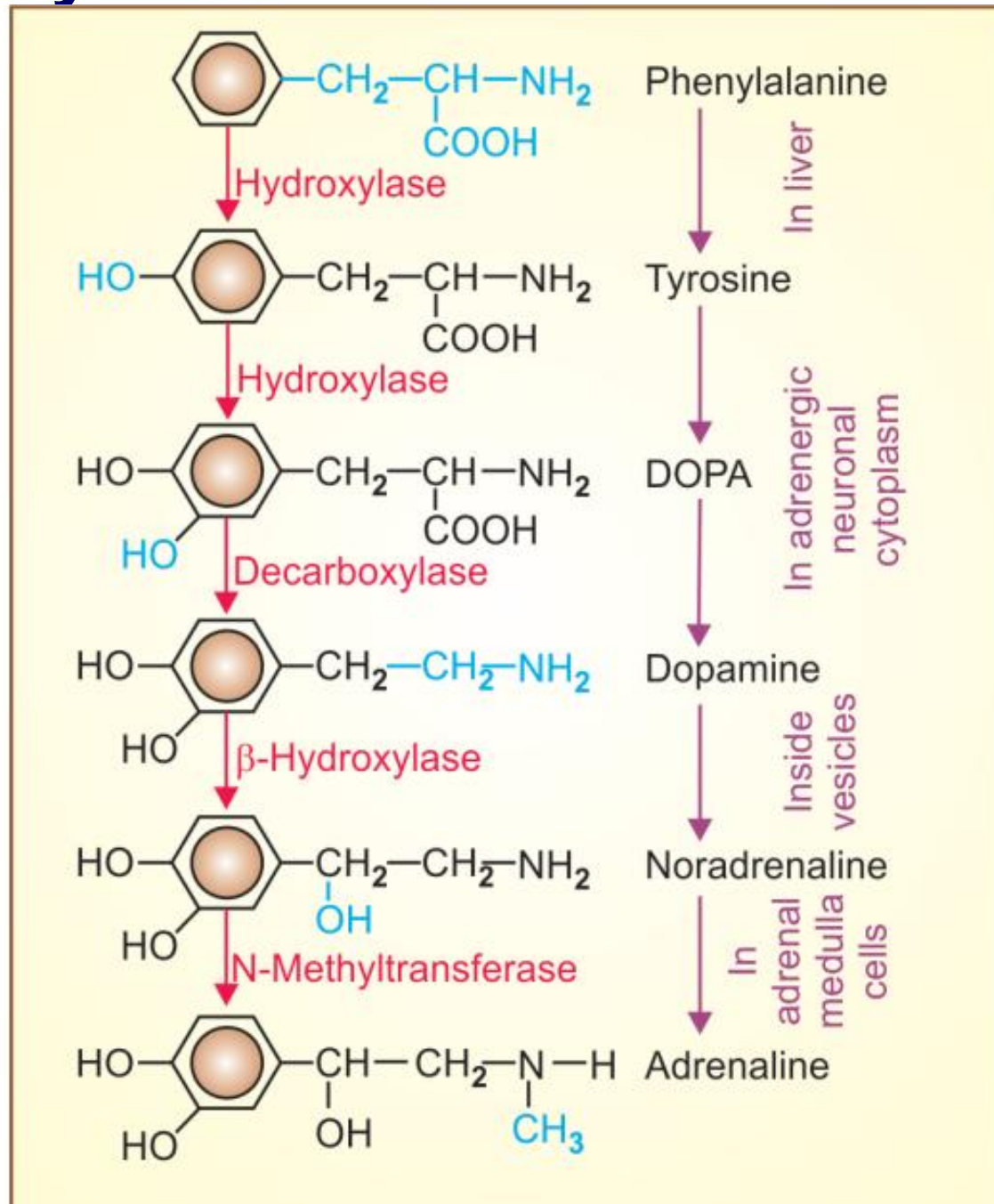
- **Neurons that release Noradrenaline (NA) substance are called adrenergic or noradrenergic neurons.**
- **Not all sympathetic postganglionic neurons are noradrenergic. The **sympathetic postganglionic** neurons that innervate the **sweat glands** and **some of the blood vessels** in skeletal muscle **are cholinergic** (they release acetylcholine rather than norepinephrine, even though anatomically they are sympathetic neurons).**

STEPS IN ADRENERGIC TRANSMISSION

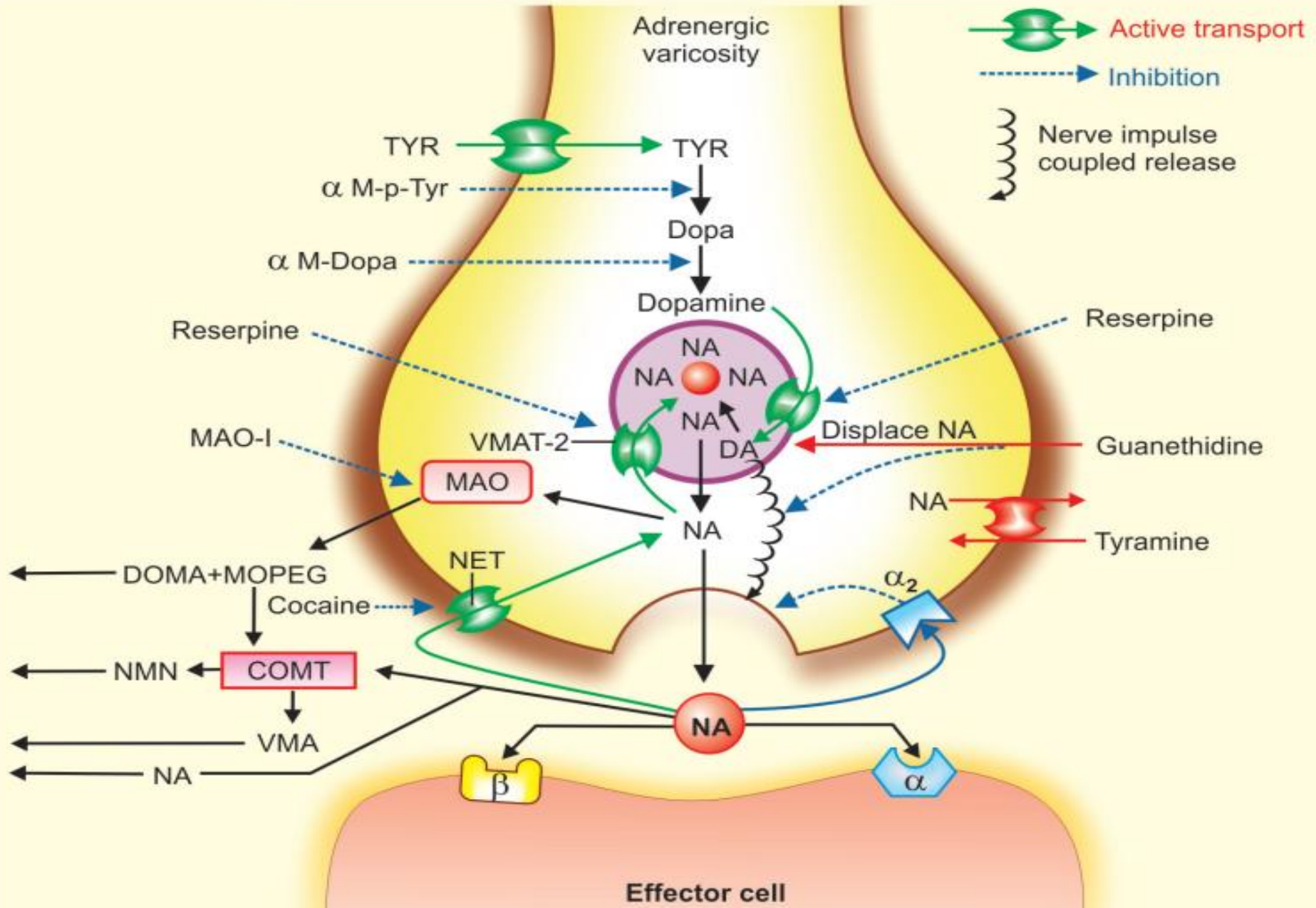
1. Synthesis of the transmitter
2. Storage of the transmitter
3. Release of the transmitter by a nerve action potential
4. Interaction of the released transmitter with receptors
5. Rapid removal of the transmitter from the vicinity of the receptors
6. Recovery of the effector cell



Synthesis of the transmitter



Removal of the transmitter



Adrenoreceptors – the receptors with which norepinephrine, epinephrine, or other adrenomimetic drugs combine.

Locations of the AR in ANS

- Cardiac muscle,
- Smooth muscles,
- Gland cells,
- Nerve terminals

Two subtypes of adrenoceptors (α and β)

- α - **excitatory** in most tissues
(except - intestinal smooth muscle)
- β - **inhibitory** in most tissues
(except - heart)

Types of adrenoceptors

- α_1 (α_{1A} , α_{1B} , α_{1D}), α_2 (α_{2A} , α_{2B} , α_{2C})
- β_1 , β_2 , β_3

Types of adrenoceptors

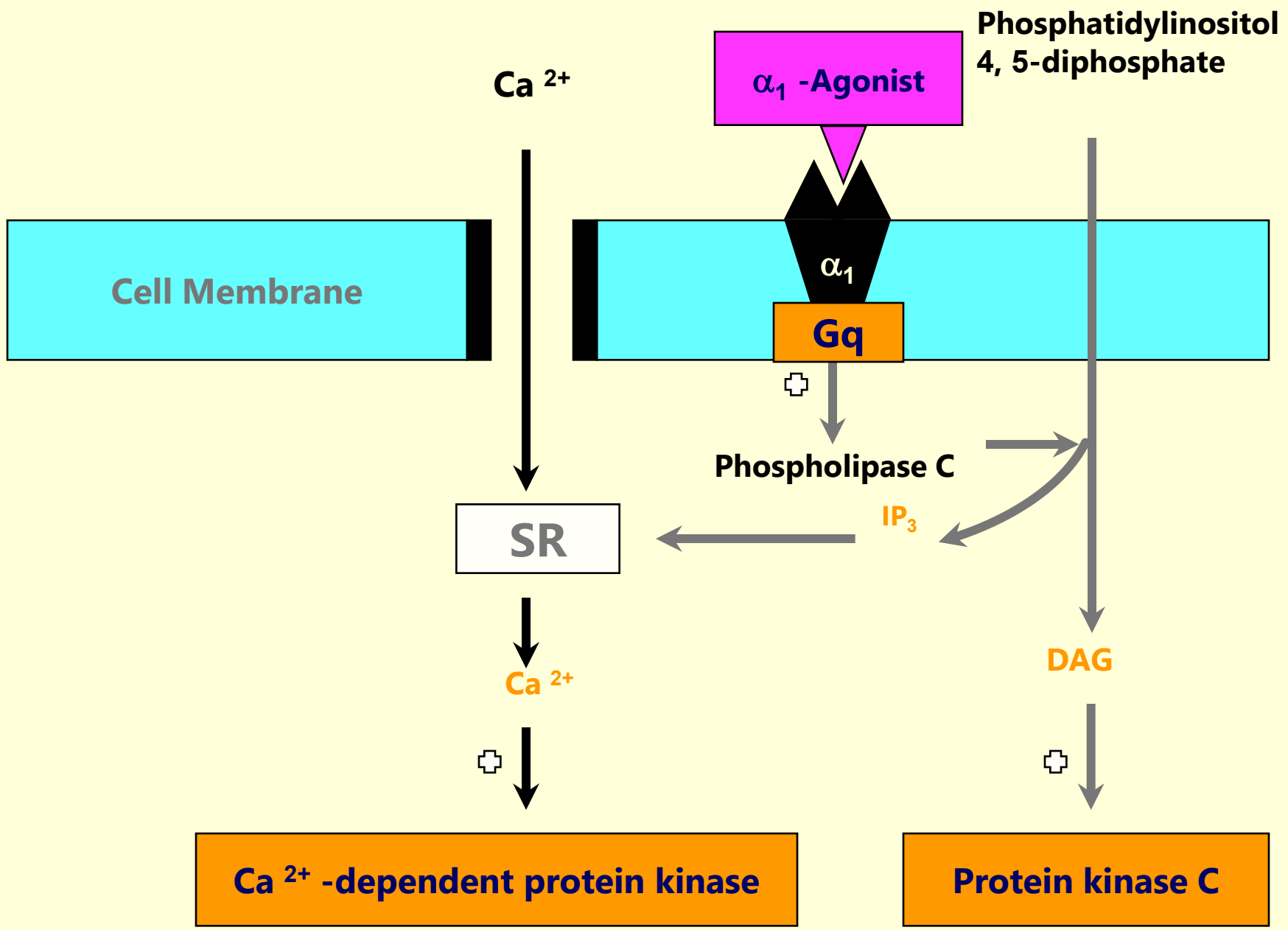
- The α_1 -adrenoceptors are located at postjunctional (postsynaptic) sites on tissues innervated by adrenergic neurons.
- α_2 -Adrenoceptors having a presynaptic location are involved in the feedback inhibition of norepinephrine release from nerve terminals.
- α_2 -Receptors also can occur postjunctionally and, more often, extrajunctionally.

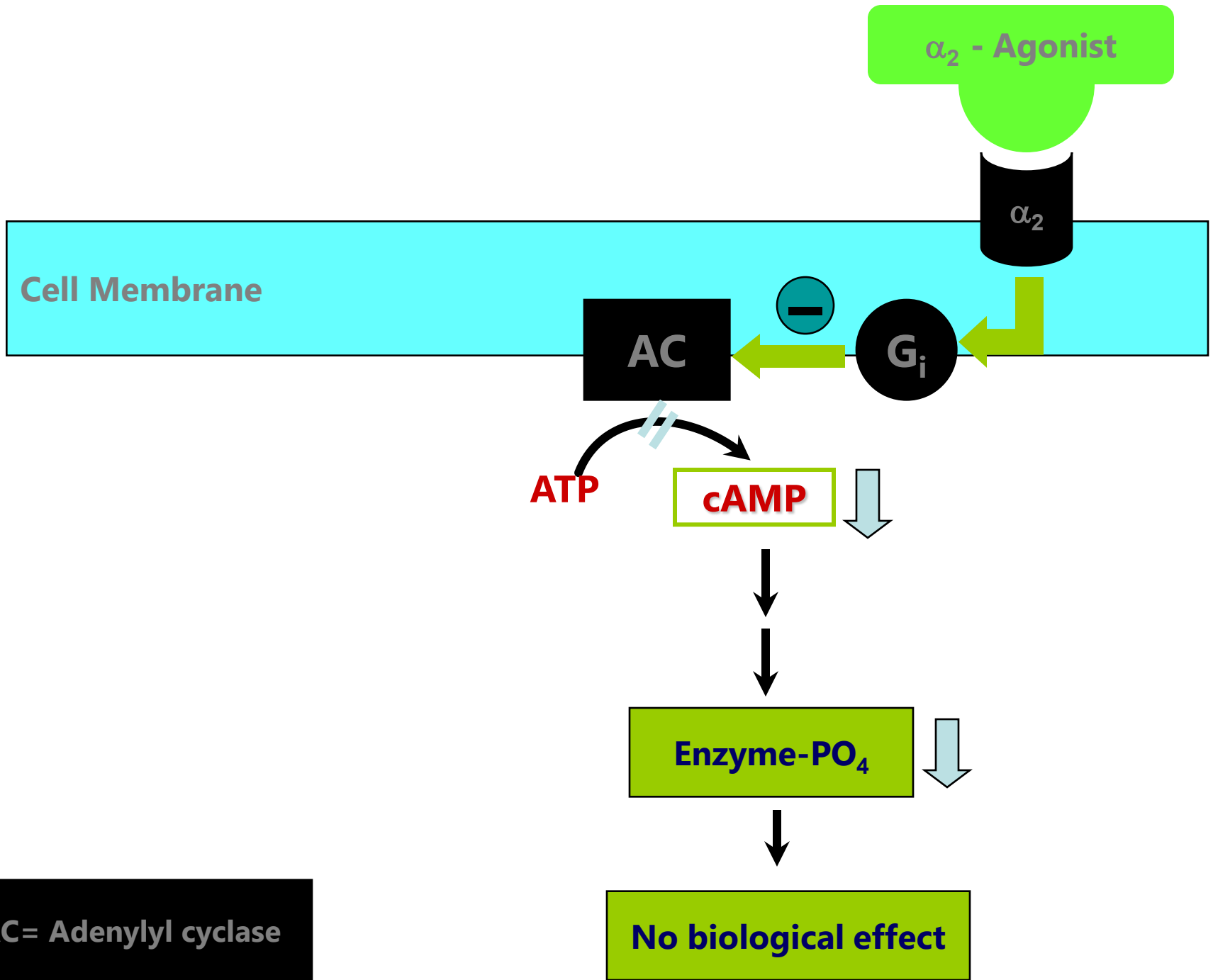
Types of adrenoceptors

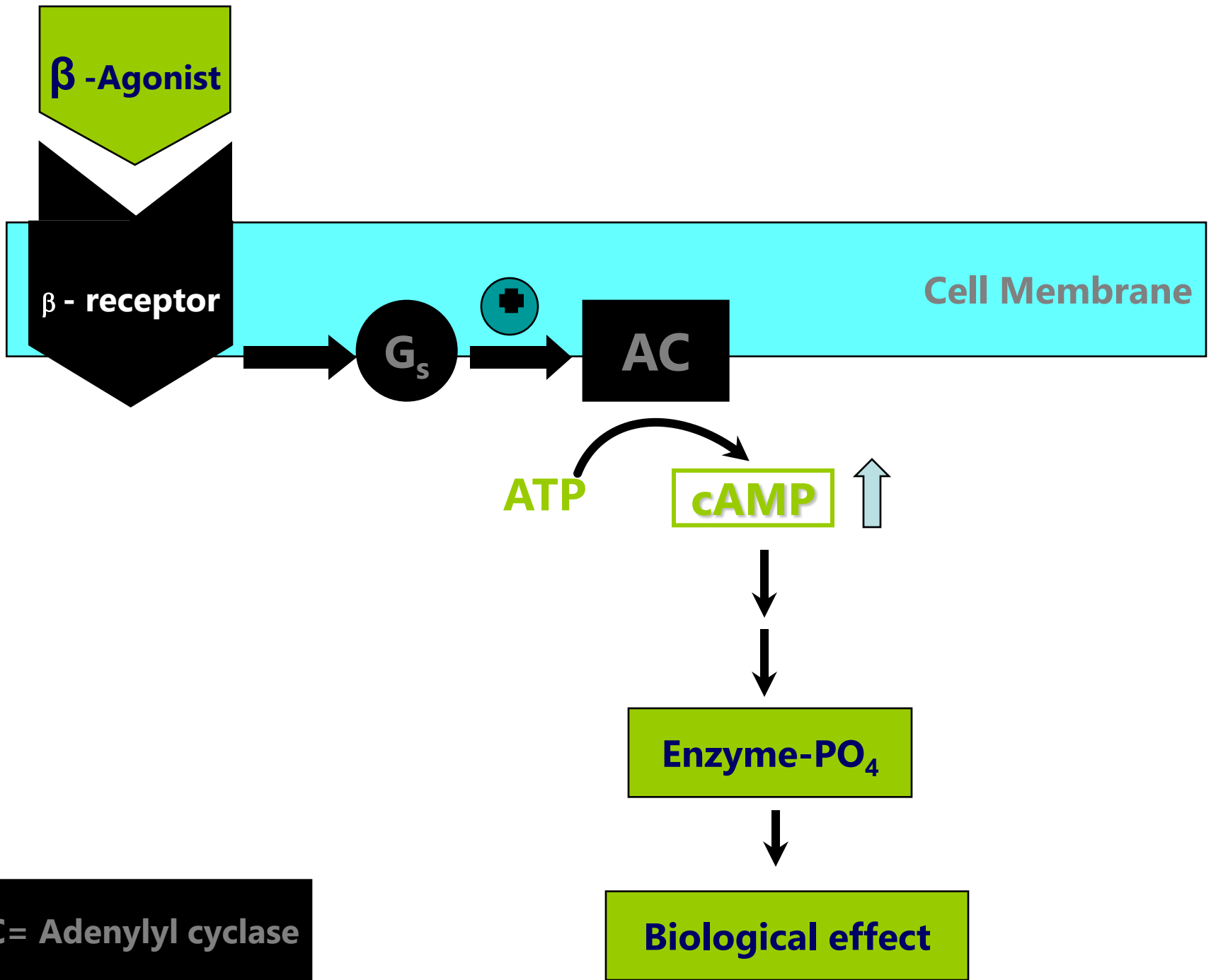
- **The β 1-adrenoceptors are found chiefly in the heart and adipose tissue, while β 2-adrenoceptors are located in a number of sites, including bronchial smooth muscle and skeletal muscle blood vessels, uterus, and are associated with smooth muscle relaxation.**
- **Presynaptic β 2-adrenoceptors are involved in the feedback activation of norepinephrine release from nerve terminals**

Mechanisms of action of adrenomimetic drugs

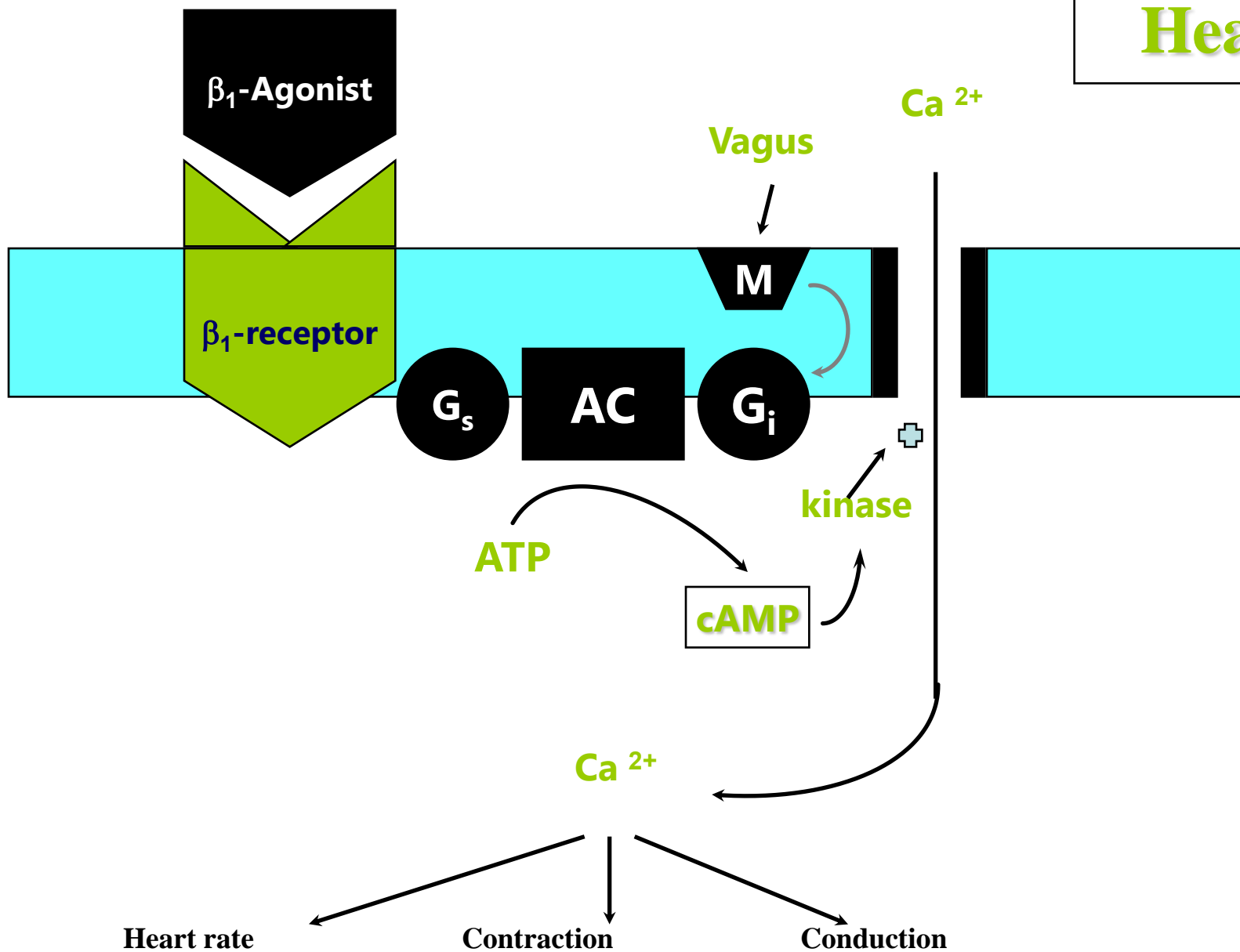
- α_1 via coupling protein G_q
- α_2 via coupling protein G_i
- $\beta_1, \beta_2, \beta_3$ via coupling protein G_s







Heart



Organ

Heart

SA node

Atrial muscle

AV node

Ventricular muscle

Effects

Rate ↑

Force ↑

Automaticity ↑

Automaticity ↑

Force ↑

Receptor

β_1

β_1

β_1

β_1

β_1

Organ

Blood vessels

Arterioles

Coronary

Skeletal muscle

Viscera

Skin

Brain

Erectile tissue

Salivary gland

Veins

Effects

Constriction/Dilation

Relaxation

Contraction

Contraction

Contraction

Contraction

Contraction

Contraction

Contraction

Relaxation

Receptor

α_1, β

β_2

α_1

α_1

α_1

α_1

α_1

α_1

α_1

β_2

Organ

Eye

Iris

IOP

Effects

Constriction of
radial muscle
causing dilation
(active mydriasis)

Decreases

Receptor

$\alpha 1$

Organ

Bronchiolar SMC

GI track

Smooth muscle

Sphincters

Effects

Relaxation

Motility, tone,
secretion ↓

Contraction

Receptor

β_2

α_2, β_2

α_1

Organ

Splenic capsule

Urinary bladder

Detrusor

Trigone

Uterus

Effects

Contraction

Relaxation

Contraction

Contraction

Relaxation

Receptor

$\alpha 1$

β

$\alpha 1$

$\alpha 1$

$\beta 2$

Organ

Skin

Pilomotor SMC

Salivary glands

Lacrimal glands

Effects

Contraction
(piloerection)

Secretion

Receptor

α_1

α_1, β_1

Organ

Kidney

Liver

**Striated
muscles**

Fat tissue

Effects

Renin release

Glycogenolysis

Gluconeogenesis

Glycogenolysis

Lipolysis

Receptor

β_1

β_2, α_1

β_2, α_1

β_2, α_1

β_3

Organ

Pancreas

Insulin release

Thrombocytes

Aggregation

Presynaptic membrane

Release of NA

Effects

Increase

Decrease

Decrease

Increase

Increase

Decrease

Receptor

β_2

α_2

β_2

α_2

β_2

α_2

Generally

- ❖ α_1 – Contraction of smooth muscle
- ❖ β_2 – Relaxation of smooth muscle
- ❖ β_1 – Stimulation in heart
- ❖ α_2 – Inhibition, for GI tract – Relaxation

- **Noradrenaline** – adrenergic transmitter
- **Adrenaline** – adrenal medullary hormone

Drugs are called:

- **Norepinephrine (NE)**
- **Epinephrine (Epi)**

- The **adrenomimetic drugs** mimic the effects of adrenergic **sympathetic nerve stimulation** (the actions of epinephrine (Epi) and/or norepinephrine) on sympathetic effectors.
- Drugs that antagonize the actions of norepinephrine are known as **adrenoceptor antagonists** (adrenoblockers, sympatholytics).

ADRENERGIC DRUGS

CL According to the site of action:

- **Drugs with direct action (on the receptors of the postsynaptic membrane):**
 - **Adrenomimetics:**
 - Norepinephrine,
 - Phenylephrine,
 - Dobutamine
 - **Adrenoblockers**
 - Phentolamine
 - Propranolol
- **Drugs with indirect action (presynaptic action, acting on release and/or storage of noradrenaline):**
 - **Indirect sympathomimetic or adrenomimetic drugs:**
 - Ephedrine
 - Pseudoephedrine
 - Tyramine
 - **Sympatholytics**
 - Reserpine
 - Guanethidine sulphate

- **Adrenomimetic drugs**
- **Adrenergic agonists**
- **Adrenoceptor agonists**
- **Sympathomimetic drugs**

Classification of adrenomimetics

According to the chemical structure

A. Catecholamines

1. Natural

- **Of animal origin**
 - Epinephrine
 - Norepinephrine
- **Of vegetal origin**
 - Ephedrine

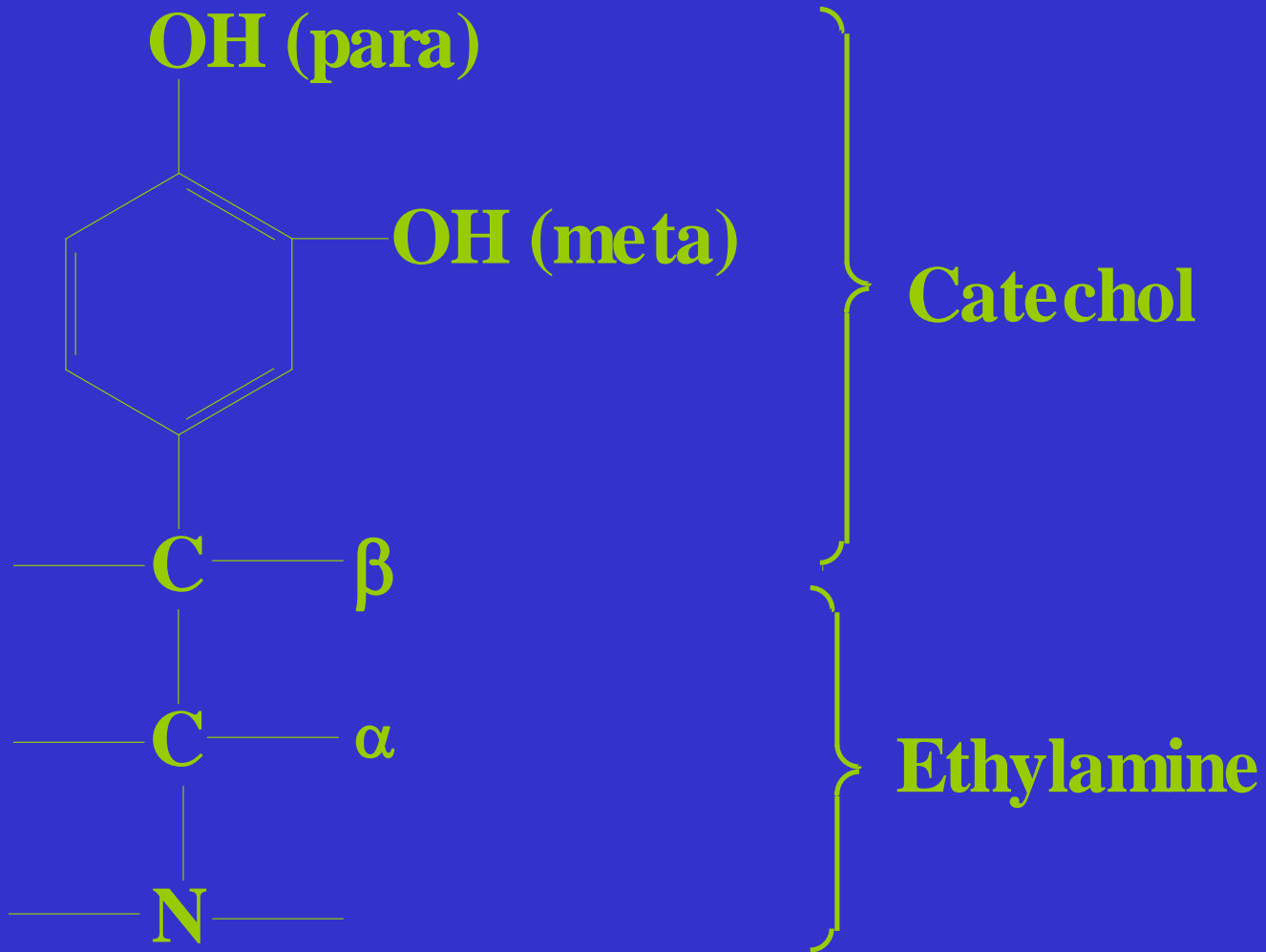
2. Synthetic

- Phenylephrine
- Ethylephrine

B. Non-catecholamines

- Naphazoline
- Xylomethazoline
- Oxymethazoline

Chemical structure of parent compound of Catecholamines



Catecholamines

- cannot be given orally
- short half-life, short duration
- high polarity
- Do not cross blood-brain barrier (BBB)
- rapid destruction by **MAO** and **COMT**
(locate at gut wall, liver)

Classification of adrenomimetics

A. Alpha-, beta-adrenomimetics

I. Direct acting

- Epinephrine (adrenaline hydrochloride)
- Norepinephrine (Nordarenaline hydrotartrate)
- Dopamine (middle dose (β) and large - (α))

II. Indirect acting (sympathomimetics)

- Ephedrine hydrochloride
- Pseudoephedrine

B. Alfa – adrenomimetics

I. With peripheral action

➤ $\alpha 1$

- Phenylephrine (Mezaton)
- Ethylephrine (Fetanol, Efortil)
- Methoxamine
- Metharaminol

➤ $\alpha 2$

- Naphazoline
- Xylometazoline hydrochloride

II. With central action

➤ $\alpha 2$

- Clonidine hydrochloride
- Dexmedetomidine
- Alfa - methyldopa

C. Beta-adrenomimetics

1. $\beta_{1,2}$

- Isoprenaline
- Orciprenaline sulphate

2. β_1

- Dobutamine hydrochloride
- Dopamine (middle dose)

3. β_2

- Terbutaline sulphate
- Salbutamol (Ventolin)
- Fenoterol
- Hexoprenaline
- Ritodrine
- Salmeterol
- Formoterol

4. β_3

- Mirabergon

Epinephrine

It stimulates:

- α 1-, α 2- (vasoconstriction, pressor effects),
- β 1- (increased myocardial contractility and conduction),
- β 2-adrenergic (bronchodilation and vasodilation) receptors.

Epinephrine Effects CVS

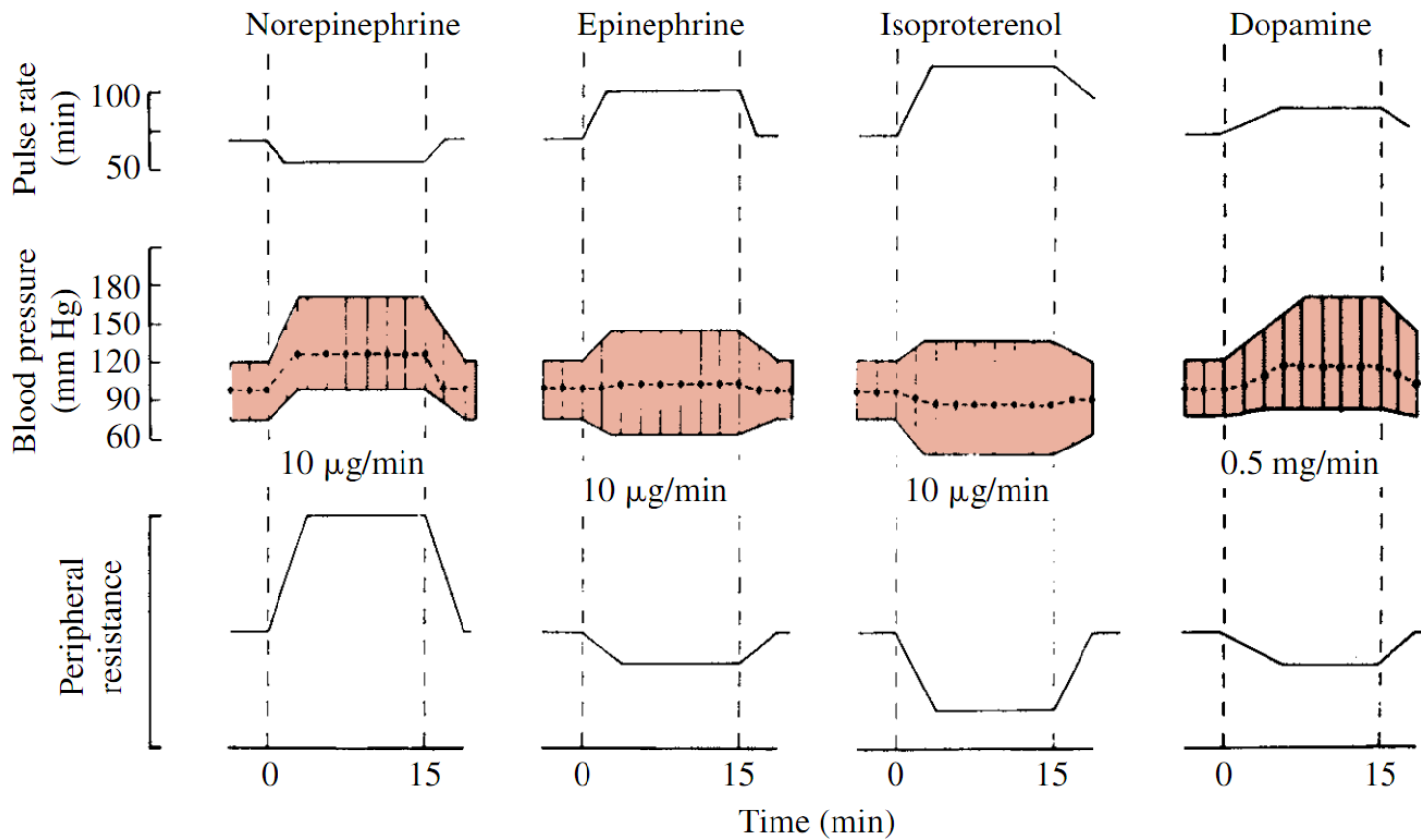
CVS

- ↑ HR, contractility, conduction,
- ↑ H excitability of VM
- ↑ Myocardial oxygen consumption
- ↑ tonus of arterioles, metarterioles, precapillary sphincters:
 - ↓ microcirculation
 - leads hypoxia, acidosis, necrosis.

Epinephrine Effects

– BP:

- I Phase \uparrow TPR and BP
- II Phase \downarrow TPR and BP



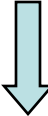
Eye

- **Radial muscle, iris (pupillary dilator)**
 - **contraction (α_1) => mydriasis**
 - **topical phenylephrine and similar alpha agonists**
 - **accommodation is not significantly affected**
 - **outflow of aqueous humor may be facilitated**
 - => reduce intraocular pressure (IOP)**
- **Ciliary muscle: relaxation for far vision (β_2)**

Respiratory System

**Relaxation of tracheal and
bronchial muscle (β_2)**

Gastrointestinal tract

- **alpha and beta receptors locate on smooth muscle and on neurons of enteric nervous system**
- **Stomach and intestine**
 -  **Motility and tone: (α_2, β_2)**
 - **Sphincters: contraction (α_1)**
 - **Secretion (intestine): inhibition (α_2): inhibit salt and water secretion**

Genitourinary tract

- **Urinary bladder**
 - **Detrusor or bladder wall: relax (β_2)**
 - **Trigone, sphincter, prostate gland: constrict (α_1)**
- **Uterus**
 - **non-pregnant: relax (β_2)**
 - **pregnant: contract (α_1), relax (β_2)**

Metabolic and hormonal effects

- **Kidney**
 - renin release (β_1)
- **Pancreatic β cells**
 - inhibit insulin release (α_2)
 - stimulate insulin release (β_2)
- **Glycogenolysis in liver and skeletal muscle (β_2) - \uparrow lactic acid (metabolic acidosis)**

Metabolic and hormonal effects

- Glucose **out of** liver associated with initially hyperkalemia, then transport into skeletal muscle resulting in a later hypokalemia.
- Lipolysis (β_3) : break down of triglycerides (TGs) into free fatty acids (FFAs) => increase lactate from lipid metabolism

Epinephrine Indications:

- Allergic reaction
- Bronchospasm and Status astmaticus
- Hypotension
- Cardiorespiratory arrest
- Severe anaphylactic shock
- Hypoglycemic coma
- Epinephrine is added to solutions of local anesthetic to:
 - **retard its absorption from the injection site:**
 - Increase duration of the anesthesia
 - Decrease toxicity of local an.
 - Reduce expense of procedure
 - **decrease bleeding**
- Open-angle glaucoma

Adverse Reactions

- **Restlessness,**
- **Anxiety**
- **Tremor**
- **Cardiac arrhythmias**
- **Palpitations**
- **Hypertension**
- **Weakness**
- **Dizziness**
- **Headache**
- **Cerebral hemorrhage**
- **Breathing difficulty,
chest pain,**
- **Angina can be precipitated
when coronary insufficiency
is present,**
- **Elevation of blood glucose**
- **Local necrosis from
repeated injections**
- **Tolerance**

Contraindications

- **Intra-arterial administration**
- **Do not use with local anesthetics in fingers or toes**
- **Do not use during general anesthesia with halogenated hydrocarbons.**
- **α -adrenergic blocker-induced hypotension;**
- **Cerebral arteriosclerosis;**
- **Organic heart disease;**
- **Cardiac dysrhythmias**
- **Narrow-angle glaucoma;**
- **Cardiogenic shock ?**
- **labor.**

Cautions

- **Cardiovascular disease**
- **Hypertension**
- **Diabetes**
- **Hyperthyroidism**
- **Psychoneurotic patients**

Norepinephrine

- α 1-, α 2- (vasoconstriction, pressor effects),
- β 1- (increased myocardial contractility and conduction),
- It has little action on β 2-receptors

Indications

- **Restoration of blood pressure in controlling certain acute hypotensive states**
(pheochromocytectomy, sympathectomy, poliomyelitis, spinal anesthesia, MI, septicemia, blood transfusion, and drug reactions)
- **Adjunct in the treatment of cardiac arrest and profound hypotension**

Adverse Reactions

- **hypertension**
- **headache**
- **reflex bradycardia**
- **increased peripheral vascular resistance**
- **decreased cardiac output**
- **volume depletion**
- **Arrhythmias can occur in extreme hypoxia or hypercarbia.**

Contraindications

- **Hypotension secondary to uncorrected blood volume deficit (hypovolemia);**
- **severe visceral or peripheral vasoconstriction;**
- **mesenteric or peripheral vascular thrombosis, unless drug is life-saving;**
- **halogenated hydrocarbon anesthesia.**

α_1 -Adrenergic receptor agonists

- Phenylephrine

– Mechanism of action

- Directly stimulate α_1 -receptors
- Phenylephrine when injected intravenously produces effects similar to NE

– Indications

- Blood pressure elevation
- Nasal decongestant
- Mydriasis induction

Clonidine

- **Stimulates postsynaptic α_2 -adrenergic receptors in the CNS by activating inhibitory neurons to decrease sympathetic outflow.**
 - **These actions reduce peripheral vascular resistance, renal vascular resistance, heart rate, and blood pressure.**
- **Sedative action**
- **Analgesic effect**

Indications

- **Hypertension**
- **Open-angle glaucoma**
- **Opiate, alcohol and tobacco withdrawal**
- **Diagnosis of pheochromocytoma**
- **As an analgesic**
- **ADHD**

Adverse Reactions

- dry mouth
- drowsiness
- dizziness
- constipation
- weakness
- sedation
- nausea or vomiting
- nervousness and agitation
- orthostatic hypotension
- sexual dysfunctions
- Rash, weight gain, anorexia, transient abnormalities in liver function tests, insomnia or vivid dreams, palpitations, tachycardia or bradycardia, or urinary retention.
- Hepatitis, thrombocytopenia, parotitis, elevations of blood glucose or CPK, or cardiac conduction disturbances.
- Allergic contact dermatitis

- **Abrupt withdrawal of oral therapy can result in a withdrawal reaction characterized by rapid reversal of the antihypertensive effect**

Dopamine

- **Precursor of epinephrine**
- **Low dose (0.5-2 mcg/kg/min): activate Dopamine receptors**
 - Dilates renal and mesenteric vessels
 - Venoconstricts
 - Arterial resistance may vary
- **Intermediate dose (2-10 mcg/kg/min): activate Beta1 receptors**
- **High dose(>10 mcg/kg/min): activate Alpha receptor**
 - Alpha effects dominate
 - Arterial and venous constriction including renal and mesenteric vessels
- **Very useful in treatment of renal failure associated with shock (low to moderate dose)**

DOPAMINE

Indications

- Cardiogenic shock
- Hemodynamically significant hypotension
- Congestive heart failure – with other agents

Dosage

- Intravenous only
- Initial infusion rate: 2 μ g/kg/min
- Increase infusion rate according to BP, urine flow response, and clinical response
- Adjust infusion rate as needed

DOPAMINE

Precautions

- Excessive vasoconstriction
- Fall in BP
- Arrhythmias
- Nausea and vomiting
- Extravasation
- Monoamine oxidase inhibitors
- Pheochromocytoma

- **EPHEDRINE**

- Hypotensive states, bronchospasm, nasal congestion, orthostatic hypotension
- Hay fever, sinusitis and allergic rhinitis
- Causes tissue necrosis in IV lines

ISOPRENALINE

Mechanisms of Action

- Pure beta-adrenergic stimulator (beta-1 and beta-2)
 - Potent inotropic effect
 - Potent chronotropic effect
- Increases cardiac output
- Increases myocardial oxygen consumption
- Vasodilation – diastolic and mean BP may fall but systolic pressure maintained or increased due to increased cardiac output
- Bronchodilation

ISOPRENALINE

Indications

- Hemodynamically significant atropine-refractory bradycardia
- Pacemaker better – as soon as possible
- Contraindicated during cardiac arrest
- Bronchospasms in asthma, bronchitis, COPD

Dosage

- 2-10 $\mu\text{g}/\text{min}$
- Titrate to increase heart rate to 60/min

ISOPRENALINE

Precautions

- Excessive tachycardia
- Arrhythmias
- Increased myocardial oxygen consumption
- Exacerbate digitalis intoxication
- Hypokalemia

DOBUTAMINE

Mechanisms of Action

- Direct beta-adrenergic stimulator
- Potent inotropic effect but less chronotropic
- Renal and mesenteric flow follows cardiac output
- Myocardial work is balanced by increases in coronary flow at clinical doses

Indications

- Congestive heart failure
- Cardiogenic shock
- Hemodynamically significant hypotension

DOBUTAMINE

Dosage

- Initial infusion rate: 0.5 μ g/kg/min IV
- Usual infusion rate 2.5-20.0 μ g/kg/min IV
- Titrated to not increase heart rate > 10%

Precautions

- Tachycardia
- Arrhythmias
- Caution in coronary artery disease

Salbutamol

- **Treat bronchospasms in asthma, bronchitis, COPD**
- **Adverse reactions: palpitations, tachycardia**
- **Drug interactions**
 - **MAO inhibitors →hypertensive crisis**
 - **Tricyclic antidepressants**
 - **B blockers**
 - **Contraindications severe heart disease, HPN, hyperthyroidism, DM**

TERBUTALINE

- B2**
- To correct bronchospasm**
- Abort preterm labor**