UNIT II

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

ADRENERGIC NEUROTRANSMITTERS

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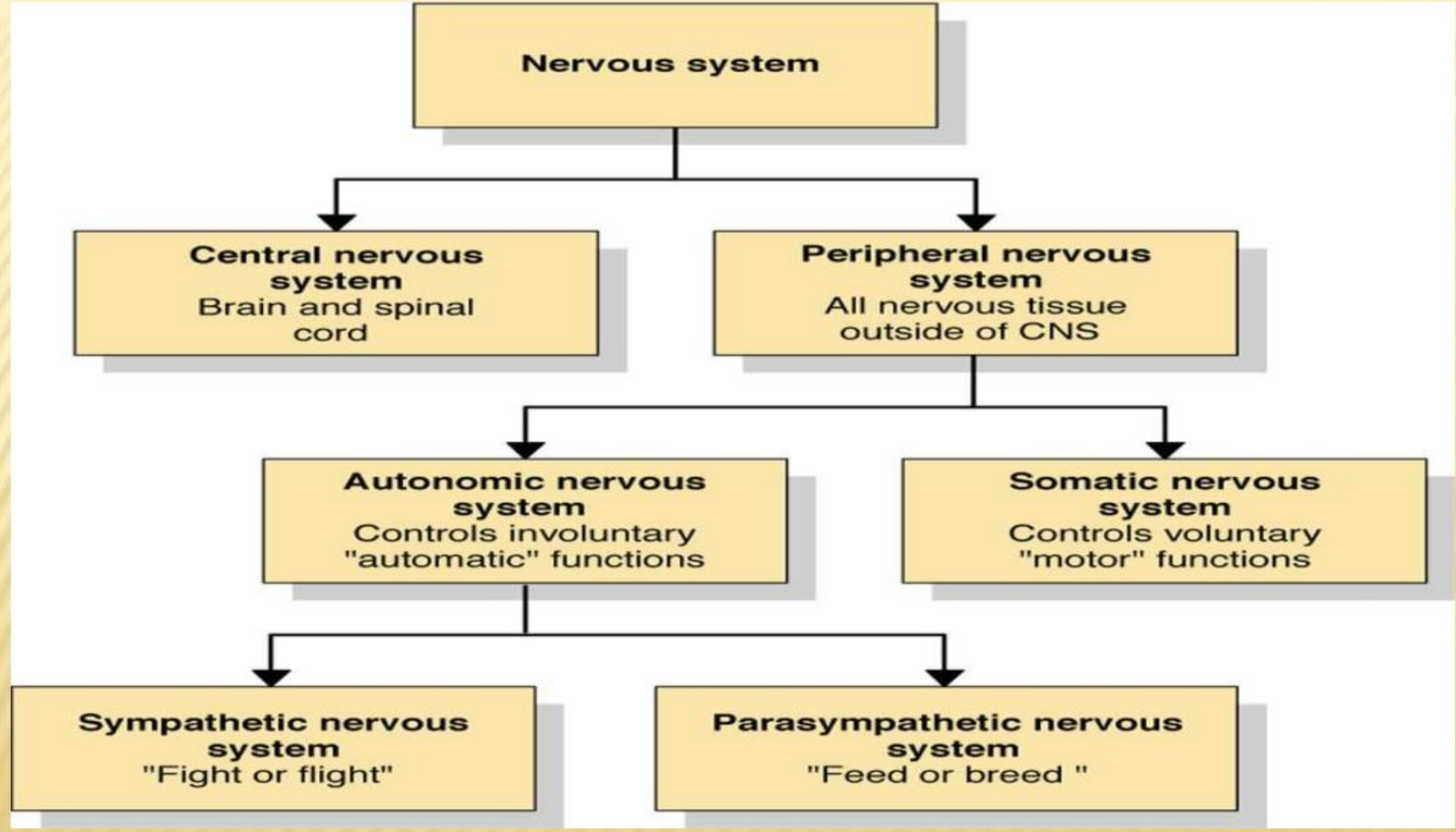
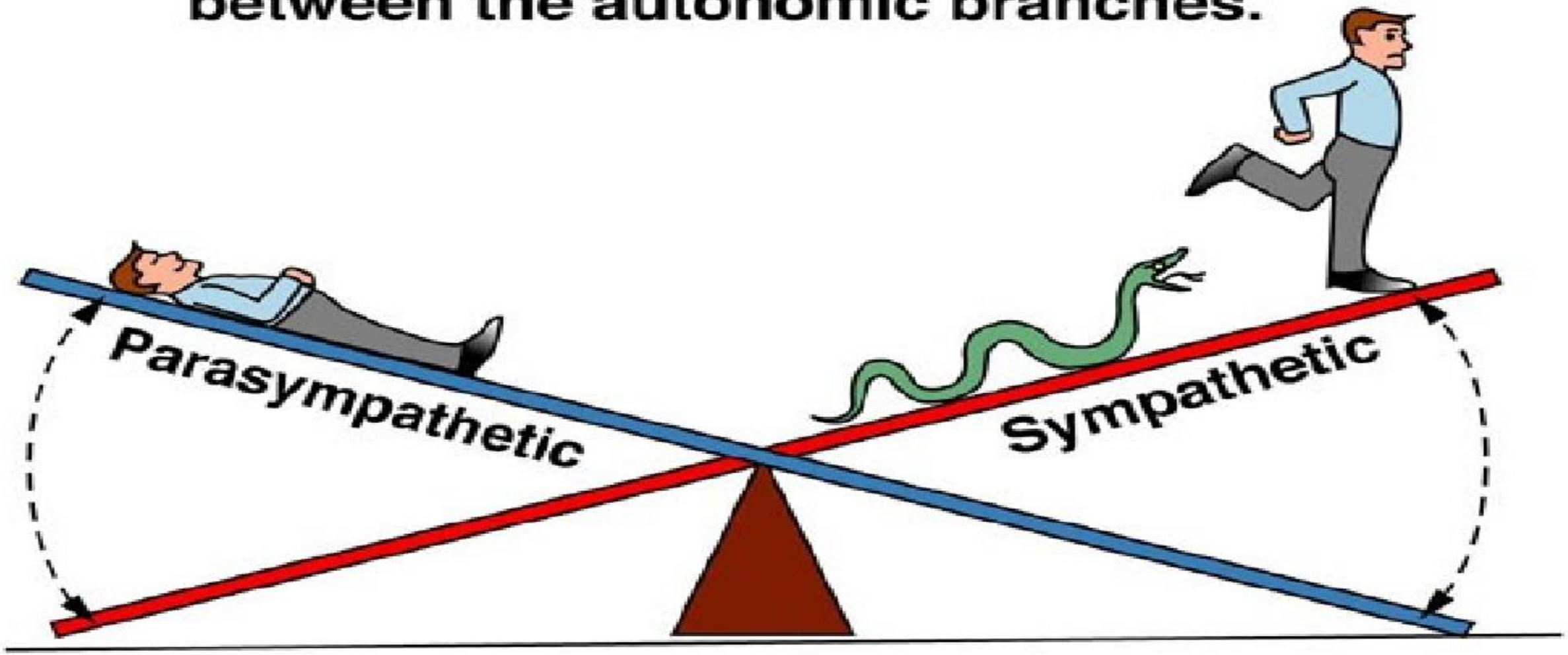

Nervous system
Central nervous system
Brain and spinal cord
Peripheral nervous system
All nervous tissue outside of CNS
Autonomic nervous system
Controls involuntary "automatic" functions
Somatic nervous system
Controls voluntary "motor" functions
Sympathetic nervous system
"Fight or flight"
Parasympathetic nervous system
"Feed or breed "

Neurotransmitters

- Sympathetic: noradrenaline (norepinephrine)
- Parasympathetic : acetylcholine

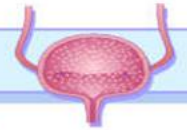
Homeostasis is a dynamic balance between the autonomic branches.



Rest-and-digest: Parasympathetic activity dominates.

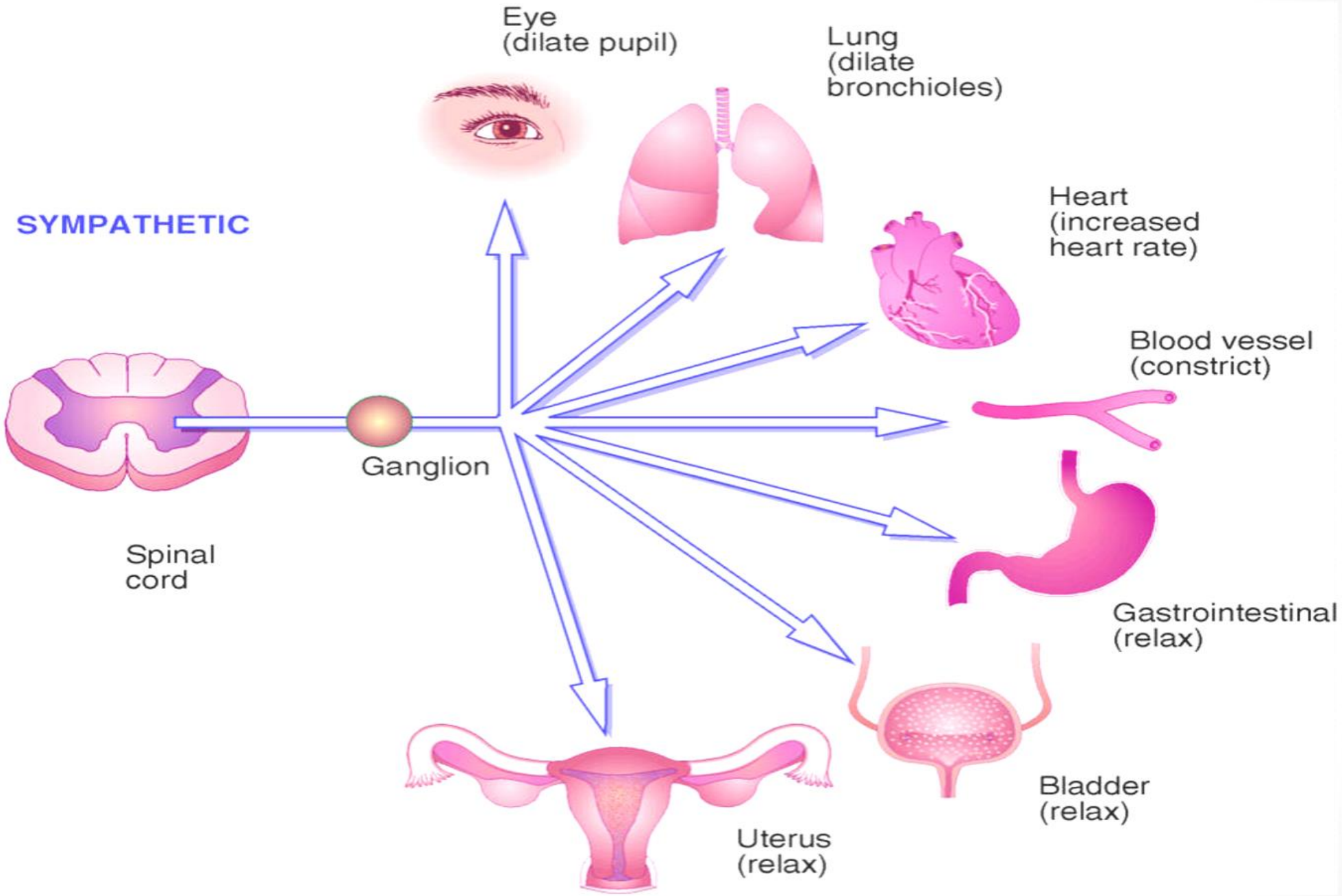
Fight-or-flight: Sympathetic activity dominates.

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.

ADRENERGIC NEUROTRANSMITTERS


Eye
(dilate pupil)
Lung
(dilate
bronchioles)
SYMPATHETIC
Heart
(increased
heart rate)
Blood vessel
(constrict)
Ganglion
Spinal
cord
Gastrointestinal
(relax)
Bladder
(relax)
Uterus
(relax)

OVERVIEW OF THE ANS

- Consists of the sympathetic and parasympathetic nervous system.
- Drugs that stimulate the sympathetic nervous system are called adrenergics.
- Adrenergics are also called adrenergic agonists or sympathomimetics because they mimic the effects of the SNS neurotransmitters norepinephrine and epinephrine (catecholamines).

INTRO

Defination:

- Compounds that produce effects similar to stimulation of sympathetic nervous activity are known as *sympathomimetic* .

Synonym: *Adrenergic stimulants*

Act by:

stimulating adrenergic receptors (adrenoceptors, ARs)

or

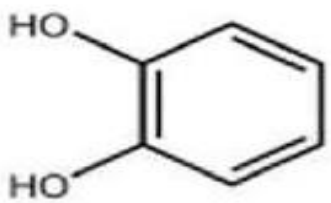
affect the life cycle of adrenergic neurotransmitters (NTs)

NEUROTRANSMITTERS

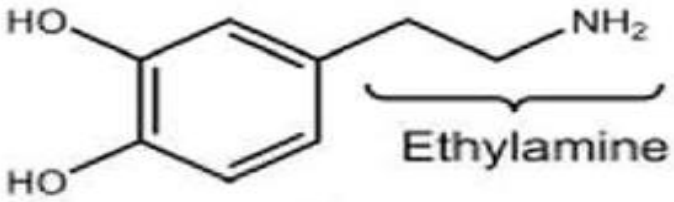
- Norepinephrine (NE, noradrenaline),
- Epinephrine (E, adrenaline) , dopamine (DA)

Structure :

- Chemically are catecholamines (CAs)



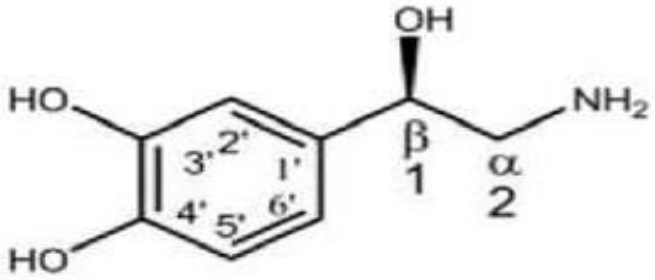
Catechol



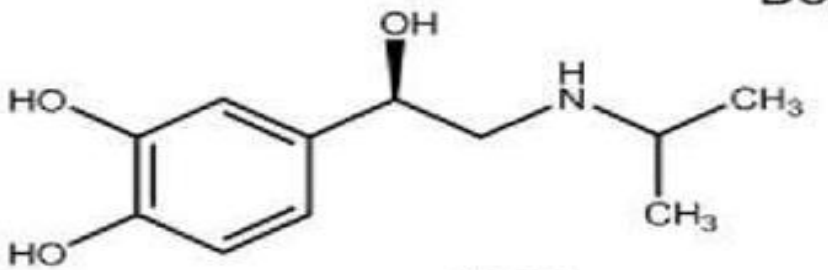
Catechol

Catecholamine

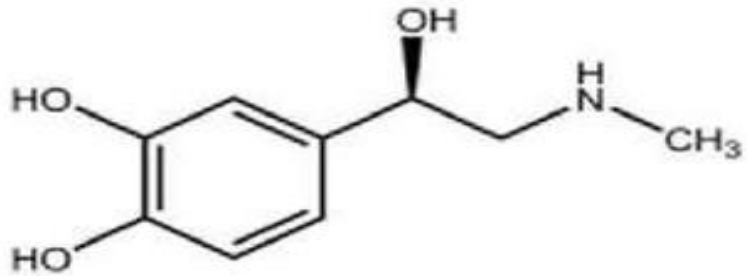
Dopamine (DA)



Norepinephrine (NE)



Isoproterenol (ISO)



Epinephrine (E)

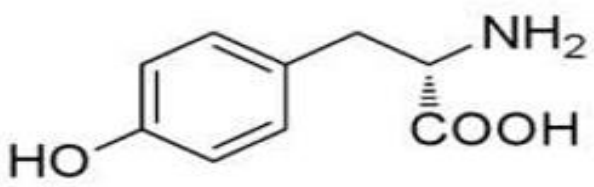
BIOSYNTHESIS &CATABOLISM OF CATECHOLAMINES

Synthesis

- The endogenous catecholamines- dopamine, noradrenaline and adrenaline are all synthesized from tyrosine.
- The tyrosine enters the adrenergic nerve via aromatic L amino acid transporter. (Na+-tyrosine symporter).
- Tyrosine hydroxylase oxidizes tyrosine to dihydroxyphenylalanine (L-DOPA).
- Aromatic L-amino acid decarboxylase converts LDOPA into dopamine.
- Dopamine enters the synaptic vesicles via vesicular monoamine transporter (VMAT) in exchange with H+ ions. Within synaptic vesicles dopamine gets converted to noradrenaline by the enzyme dopamine-β-hydroxylase. Dopamine is the neurotransmitter in the dopaminergic neurons.
- Noradrenaline is the main NT in the adrenergic neurons. But in the adrenal medulla noradrenaline is converted into adrenaline by the enzyme phenylethanolamine N-methyl transferase (PNMT). Hence **adrenaline is the main NT in the adrenal medulla.**

NEUROCHEMISTRY

Biosynthesis :

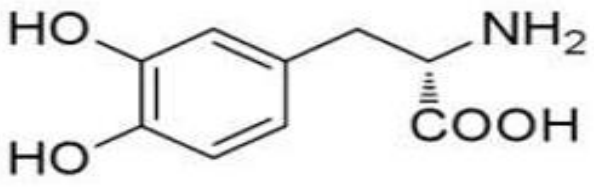


L -Tyrosine

Tyrosine Hydroxylase

rate-limiting step

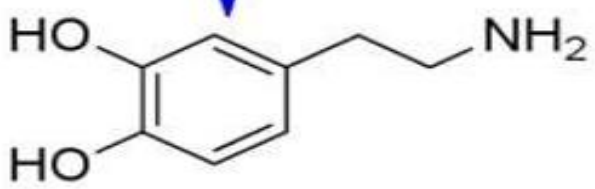
Step_1



L - DOPA

Step_2

DOPA decarboxylase

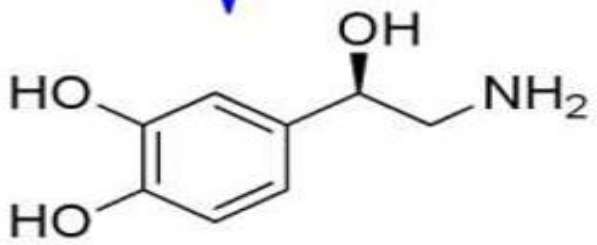


Dopamine

(*R*) Configuration of NE and E

Step_3

dopamine β-hydroxylase

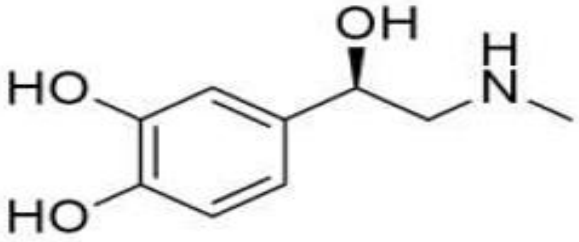


Norepinephrine

Phenylethanolamine-N-methyltransferase

(adrenal medulla)

Step_4



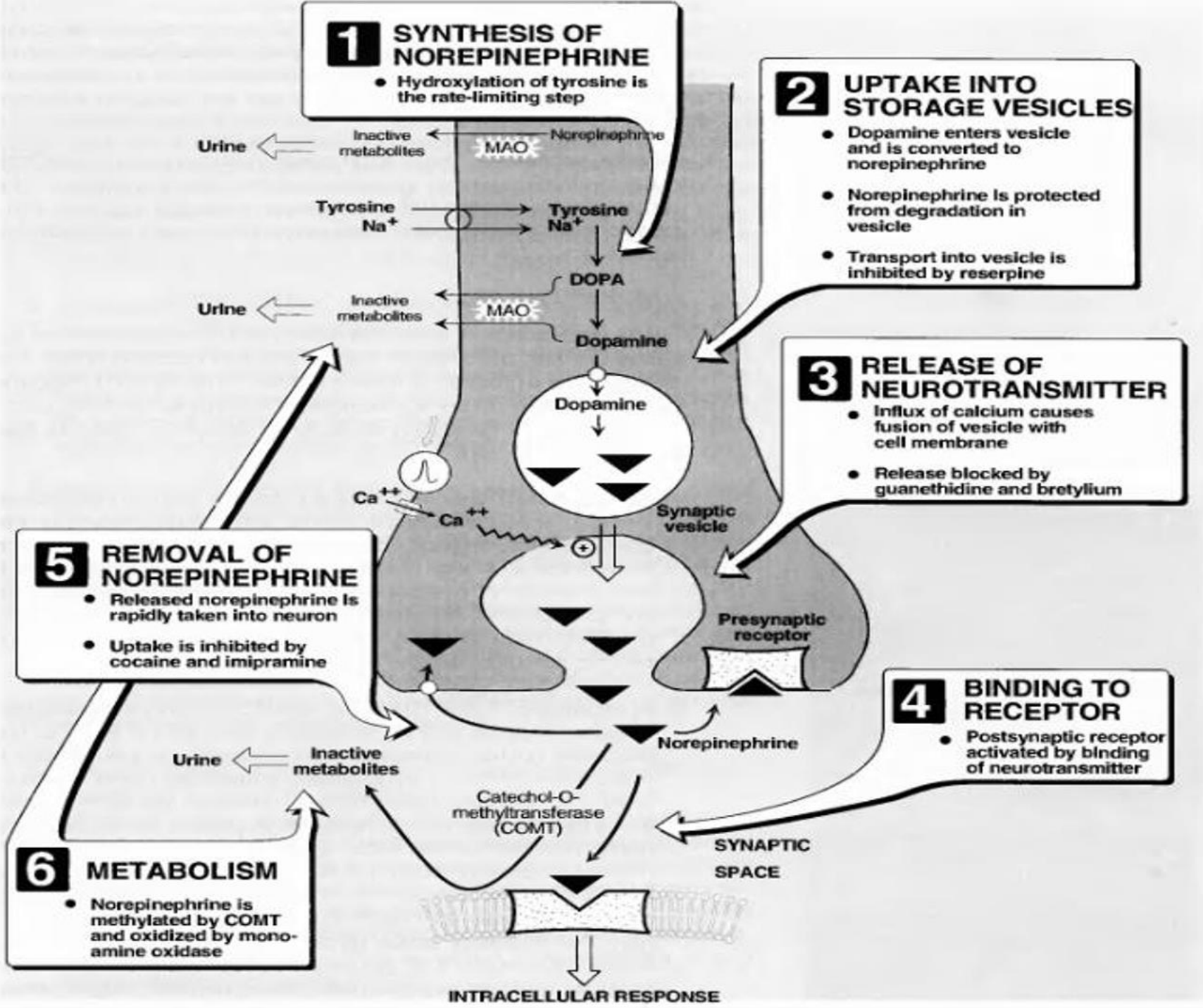
Epinephrine

Release

- On arrival of an impulse at the adrenergic nerve ending, the voltage gated calcium channels get opened.
- This leads to influx of calcium ions.
- The triggered calcium causes rupture of synaptic vesicles by a process called exocytosis.
- This releases the noradrenaline into the synaptic cleft (NEJ-neuro effector junction). The noradrenaline binds to the alpha receptors or beta receptors present on the presynaptic or post synaptic membrane.
- This initiates the pharmacological response.

METABOLISM

- Noradrenaline is metabolized by two main enzymes- Catechol-o-methyl transferase (COMT) and monoamine oxidase (MAO).
- COMT is present in the circulating blood and this enzyme degrades the circulating catecholamines.
- Whereas MAO is located in the adrenergic neurons and this degrade the noradrenaline located in the adrenergic nerves (outside the vesicles).
- COMT, MAO and aldehyde dehydragenase degrade the catecholamines into multiple intermediates and finally into vanillyl mandelic acid (VMA), which is excreted through urine.
-


1 SYNTHESIS OF NOREPINEPHRINE
• Hydroxylation of tyrosine is the rate-limiting step
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
Tyrosine
Na+
DOPA
Urine
Inactive metabolites
MAO
Dopamine
2 UPTAKE INTO STORAGE VESICLES
• Dopamine enters vesicle and is converted to norepinephrine
• Norepinephrine is protected from degradation in vesicle
• Transport into vesicle is inhibited by reserpine
Dopamine
3 RELEASE OF NEUROTRANSMITTER
• Influx of calcium causes fusion of vesicle with cell membrane
• Release blocked by guanethidine and bretylium
Ca++
Ca++
Synaptic vesicle
5 REMOVAL OF NOREPINEPHRINE
• Released norepinephrine is rapidly taken into neuron
• Uptake is inhibited by cocaine and imipramine
Presynaptic receptor
4 BINDING TO RECEPTOR
• Postsynaptic receptor activated by binding of neurotransmitter
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
6 METABOLISM
• Norepinephrine is methylated by COMT and oxidized by mono-amine oxidase
INTRACELLULAR RESPONSE

ADRENERGIC RECEPTORS

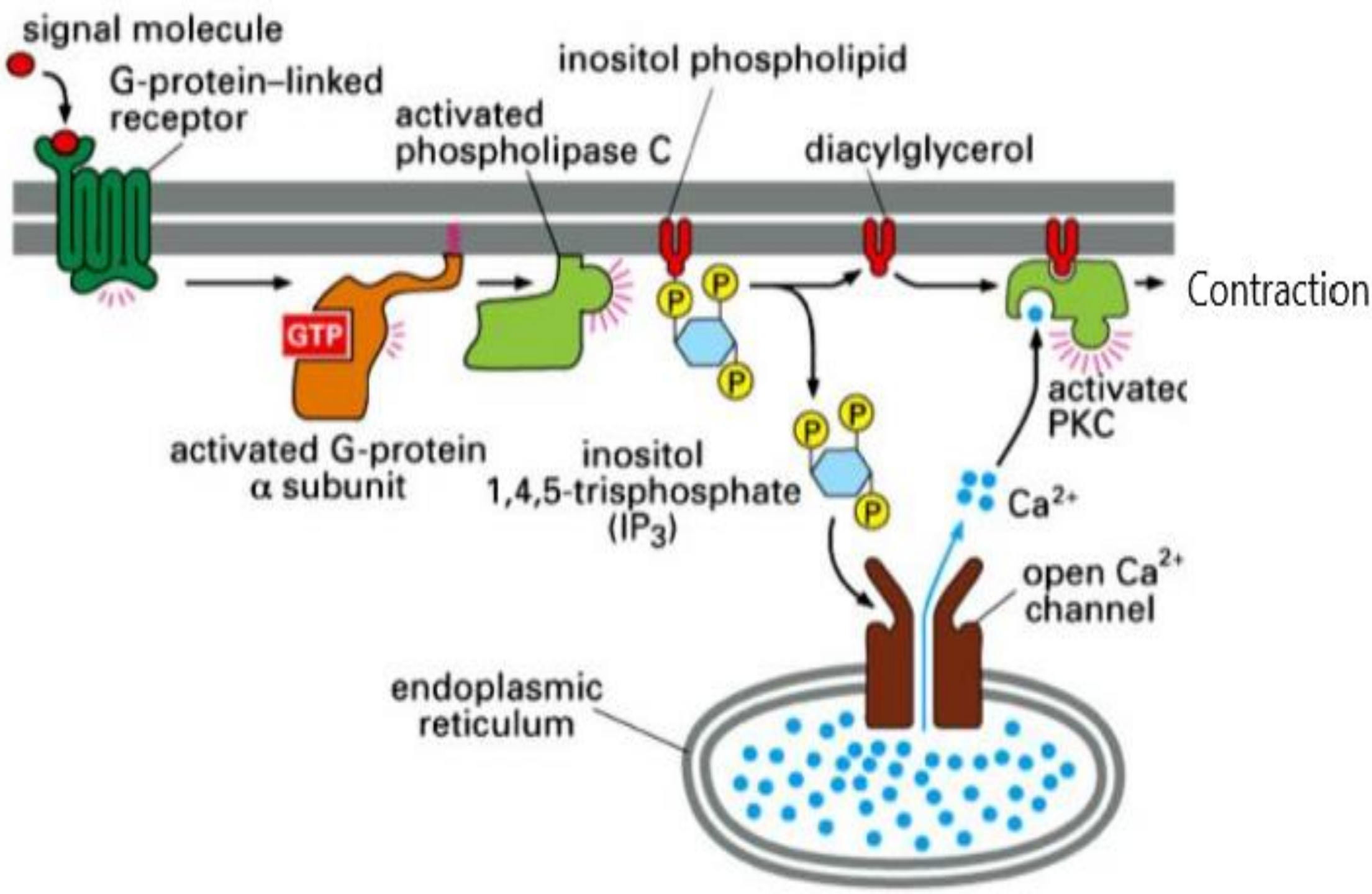
- Adrenergic receptors are the sites where adrenergic drugs bind and produce their effects.
- Adrenergic receptors are divided into alpha-adrenergic and beta-adrenergic receptors depending on whether they respond to norepinephrine or epinephrine.
- Both alpha- and beta-adrenergic receptors have subtypes designated 1 and 2.

Adrenergic receptors- (adrenoceptors) are selective for nor adrenaline and adrenaline.

There are two types- α-adrenoceptors and β-adrenoceptors.

1). **α-adrenoceptors**- They are divided into α1 and α2 subclasses.

- α1 adrenoceptor is a G protein coupled receptor (GPCR) associated with Gq type of G protein.
- When adrenaline binds to this receptor, GDP converted to GTP.
- The -GTP complex binds to the membrane bound phospho lipase-C (PLC).
- The activated PLC converts membrane phospholipids phosphatidylinositol-4,5bisphosphate (PIP2) into inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG).
- The DAG remains in the membrane and activates protein kinase C (PKC).
- The activated PKC phosphorylates several cellular proteins.
- IP3 stimulates the release of calcium from ER into the cytosol.
- The released calcium ions are responsible for the action.
- The calcium ions bound to the calmodulin protein (CaM). Ca2+- CaM complex activates the MLCK (Myosin light chain kinase).
- The activated MLCK causes the phosphorylation of myosin-LC.
- The myosin-LC-P causes smooth muscle contraction


signal molecule
G-protein–linked receptor
activated phospholipase C
inositol phospholipid
diacylglycerol
Contraction
GTP
activated G-protein α subunit
inositol 1,4,5-trisphosphate (IP_3)
activated PKC
Ca^{2+}
open Ca^{2+} channel
endoplasmic reticulum

Important locations of α1 adrenoceptors- Vascular smooth muscles, genitourinary smooth muscle, radial muscle, intestinal smooth muscle, heart and liver (Except intestine all actions are excitatory).

a)Vascular smooth muscles- Vasoconstriction (MOA as above).

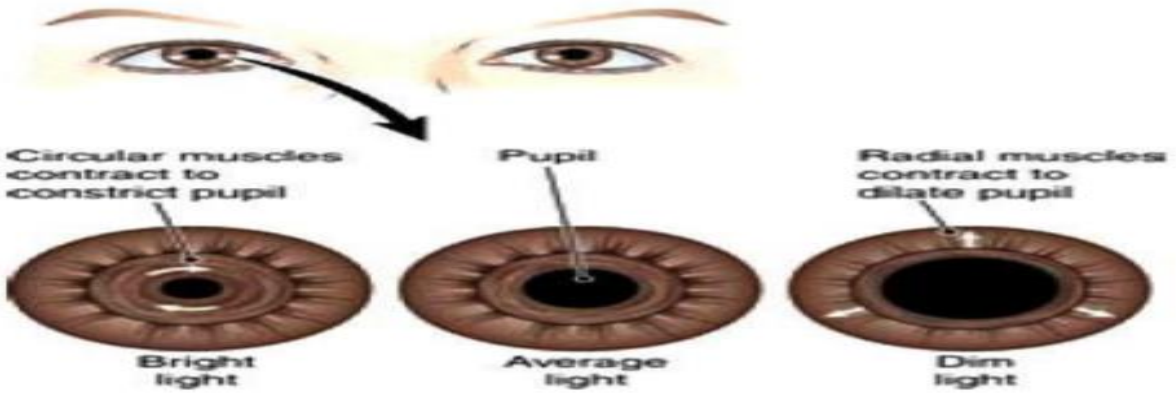
b) Genitourinary smooth muscles- Contractions (MOA as above).

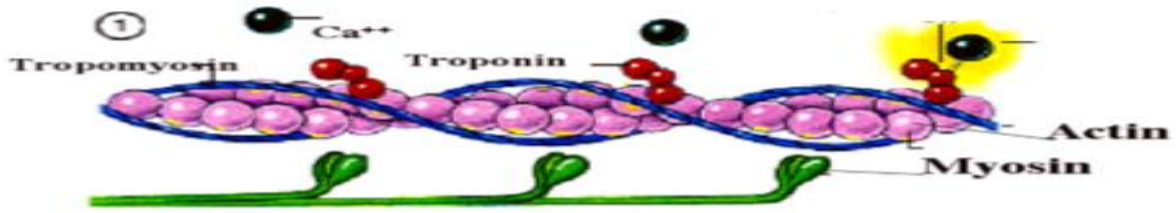
c)Radial muscle- Contraction –mydriasis (MOA as above).

d) Heart- Increases the rate and force of heart contraction. MOA- The calcium ions bind to the troponin, this leads to the interaction of actin-myosin causing heart muscle contraction.

e) Liver- Increases glycogenolysis and gluconeogenesis. MOA- DAG causes activation of PKC. The activated PKC causes the phosphorylation of enzymes needed for glycogenolysis and gluconeogenesis.

f) Intestinal muscles- Relaxation. The activated protein kinase causes phosphorylation of cellular proteins. For eg K+ channel activation leads to efflux of K+ ions leading hyperpolarization (IPSP). The IPSP is also due to inactivation of calcium channels.





α2 adrenoceptor- is a G protein coupled receptor (GPCR) associated with Gi type of G protein.

- When adrenaline binds to this receptor, GDP converted to GTP, αβγ subunits of G protein gets detached.
- The α-GTP complex binds to the membrane bound adenylyl cyclase (AC).
- The inhibited AC decreases the formation of cAMP. The α-GTP complex also activates the K+ channel.
- This increases the removal of K+ ions from the cell to outside.
- This decreases the potential inside the cell (hyperpolarization).
- The α-GTP complex also inactivates the Ca2+ channels.
- This decreases the influx of Ca2+ ions into the cell.
- This also decreases the potential within the cell causing hyperpolarization. Hence the action is inhibition.

Important locations of α2 adrenoceptors-

Pancreatic β cells, platelets, nerve, vascular smooth muscles. (all actions are inhibitory except vascular smooth muscle).

a) Pancreatic β cells- Decreases insulin secretion.

b)Platelets- Aggregation.

c)Nerve- Function as auto-receptors, neuronal inhibition.

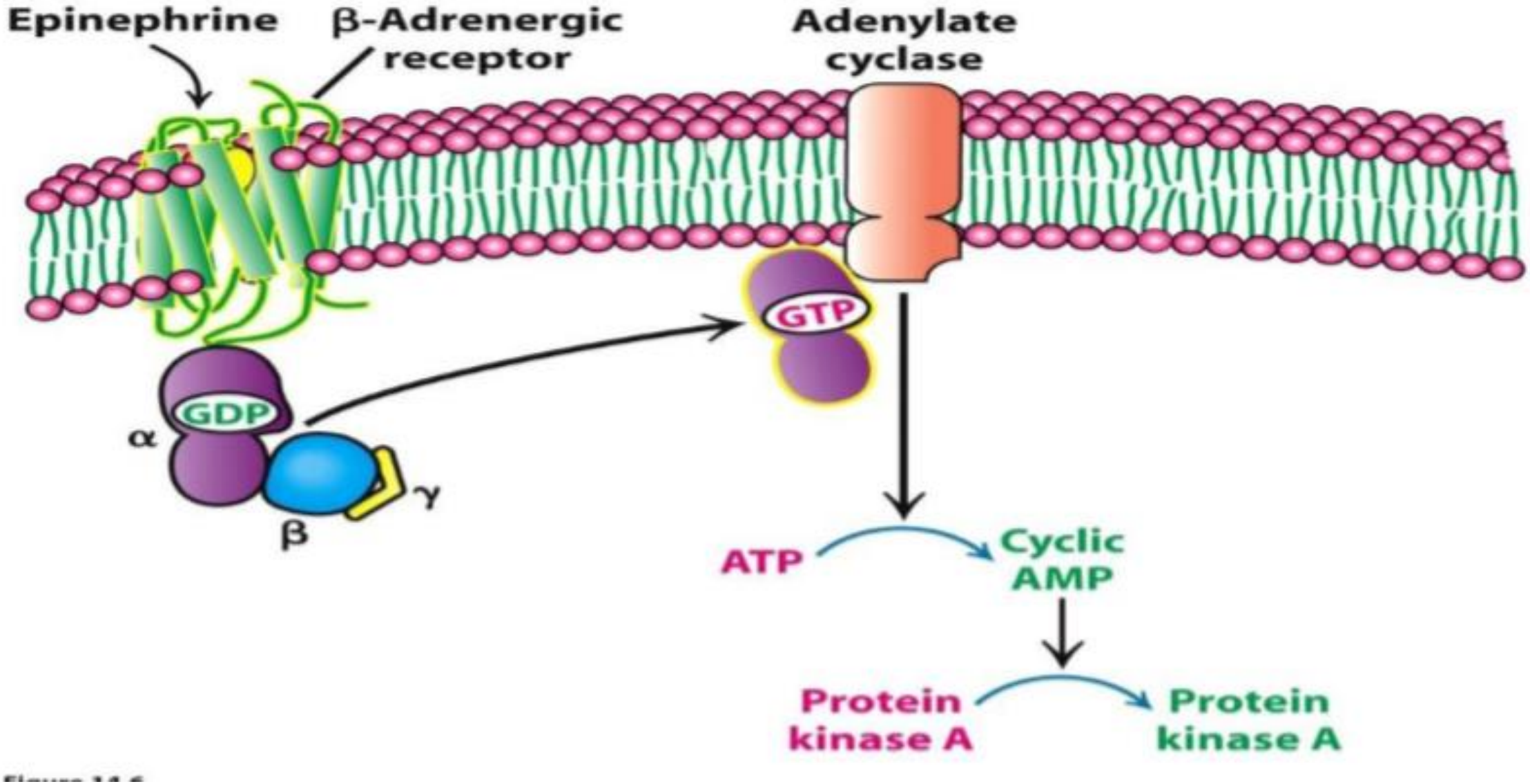
d)Vascular smooth muscle- Vasoconstriction (both α1 and α2 causes vasoconstriction)

β-adrenoceptors

These are divided into three types- **β1, β2 and β3**.

All three belongs to stimulatory (Gs) type of G protein coupled receptors. β-adrenoceptor is a G protein coupled receptor (GPCR) associated with Gs type of G protein. When adrenaline binds to this receptor, GDP converted to GTP, αβγ subunits of G protein gets detached. The α-GTP complex binds to the membrane bound adenylyl cyclase (AC). The stimulated AC increases the formation of cAMP. Increased cAMP activates protein kinases (especially protein kinase A), which phosphorylates cellular proteins, including ion channels.

- β1 receptors located on heart (SAN and myocardium), renal juxta glomerular cells. Increases the heart rate (chronotropy) and force of heart contraction (inotropy) and increases the rennin secretion.
- β2 receptors are located in smooth muscles, liver, and skeletal muscles. Stimulation of β2 receptors in bronchial smooth muscles causes bronchodilatation. This effect is due to Gs independent activation of K+ channels resulting in hyperpolarization. This relaxes the bronchial smooth muscles. In liver stimulation of β2 receptors results in increased blood sugar level. In skeletal muscle β2 receptors results in increased glycogenolysis.
- β3 receptors are located in adipose tissue. In adipose tissue stimulation of β3 receptors results in increased lipolysis.


Epinephrine
β-Adrenergic receptor
Adenylate cyclase
GTP
GDP
α
γ
β
ATP
Cyclic AMP
Protein kinase A
Protein kinase A

THANK YOU