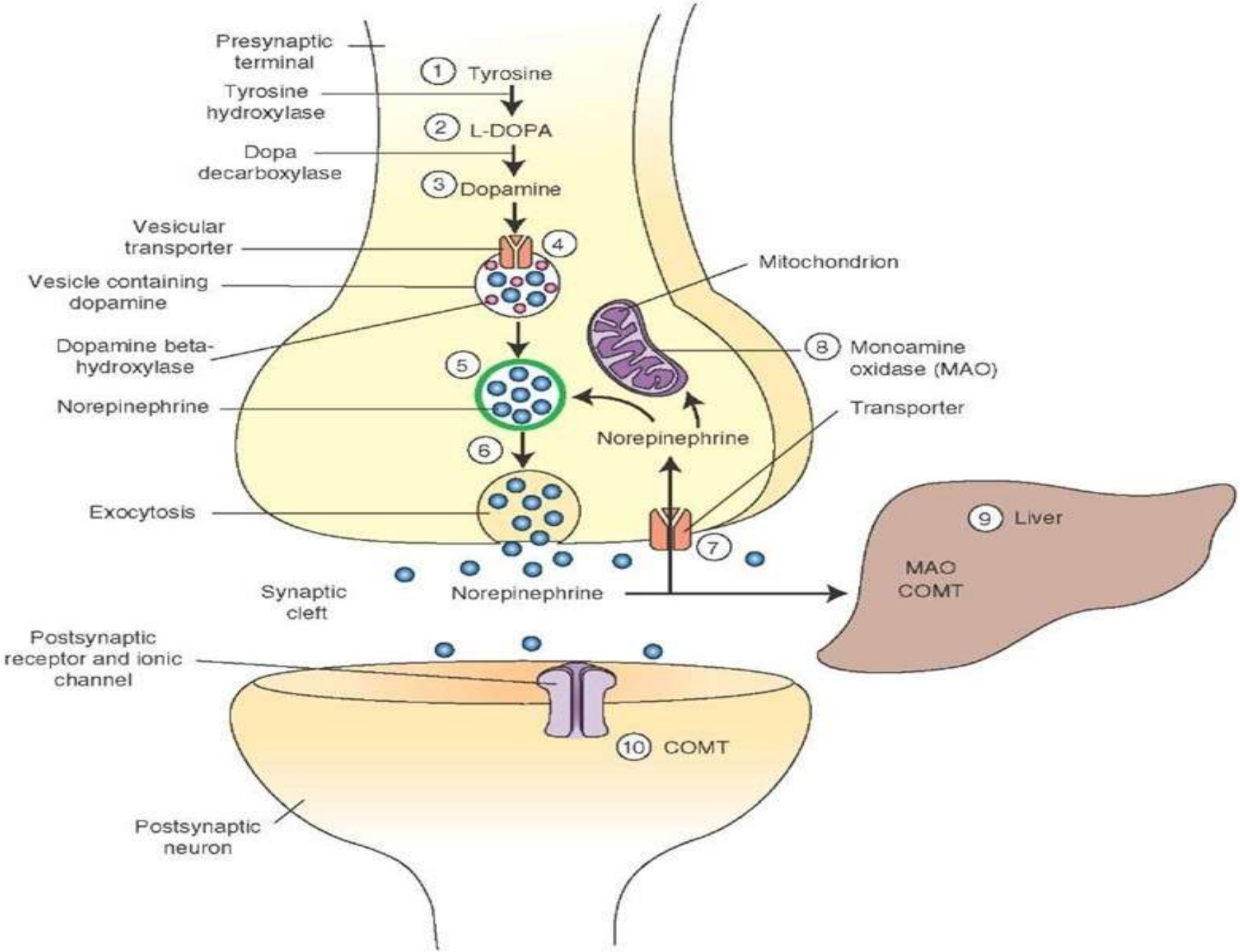
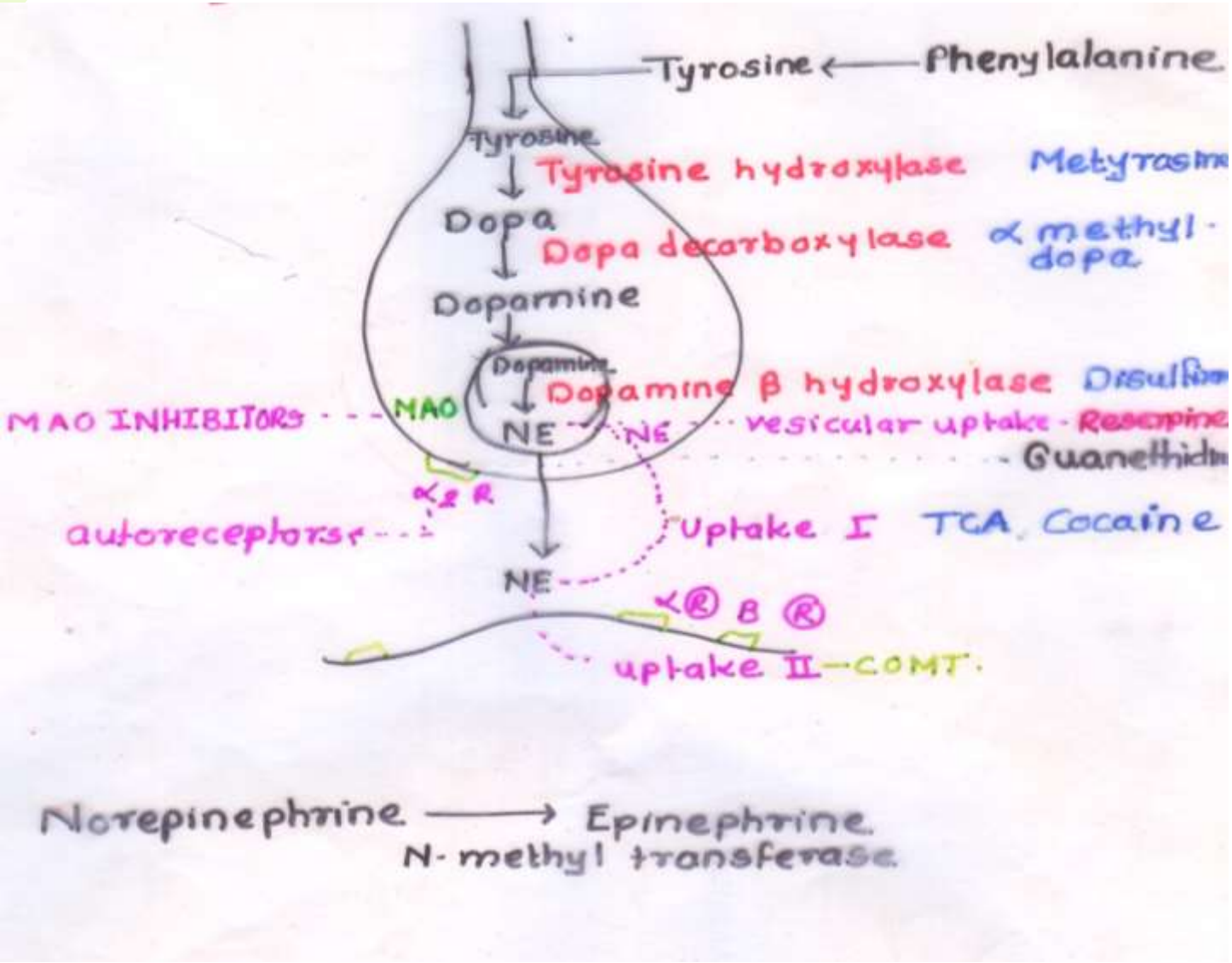
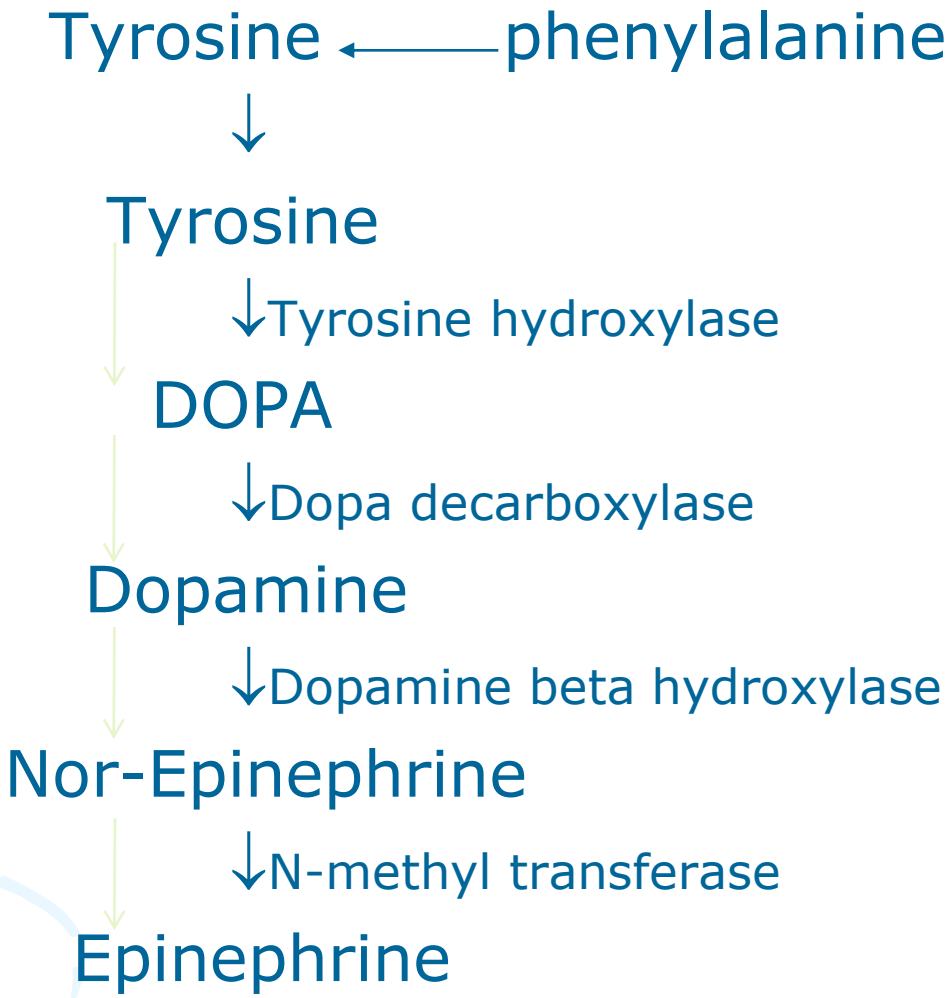
Adrenergic Drugs/ Sympathomimetic Agents


Presynaptic terminal
Tyrosine hydroxylase
Dopa decarboxylase
Vesicular transporter
Vesicle containing dopamine
Dopamine beta-hydroxylase
Norepinephrine
Exocytosis
1 Tyrosine
2 L-DOPA
3 Dopamine
4
5
6
Mitochondrion
8 Monoamine oxidase (MAO)
Transporter
Norepinephrine
7
9 Liver
MAO
COMT
Synaptic cleft
Norepinephrine
Postsynaptic receptor and ionic channel
10 COMT
Postsynaptic neuron

Synthesis of NE



Synthesis of NE



- Uptake I

  Axonal uptake (Nearly 80 percent)

  Active amine pump-neuronal membrane-transport of NE

- Uptake II

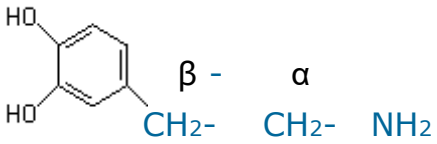
  Extra neuronal uptake

- Metabolism

  MAO,COMT

1. Catecholamines
2. Noncatecholamines

Parent compound β phenylethylamine

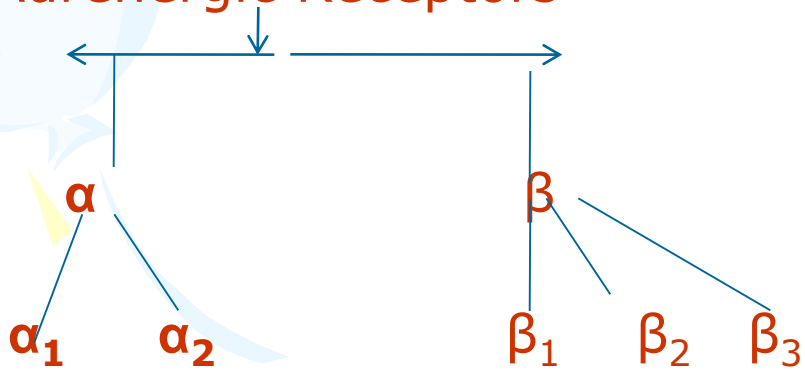


Catecholamines	Noncatecholamines
Presence of catechol nucleus	**- Lack one or both OH groups**
Benzene ring with "OH" groups	**- OH group at other position**
At 3 & 4 position	**- Other group substitution.**
Very potent at both types Of receptor (α&β)	**Absence of ' OH' at 3 & 4 benzene ring –Decrease overall potency at receptor.**
Can't cross BBB	**Can cross BBB Action on CNS +**

Metabolized by MAO & COMT	Resistant
Can't be given orally	can be given orally
Direct action	Direct + Indirect

Natural- NE, Adrenaline, Dopamine
Synthetic -Dobutamine

Adrenergic Receptors



Excitatory Inhibitory

Second messenger system

β Receptor

G_s protein → + Adenylyl cyclase - cyclic AMP –Protein kinase protein phosphorylation

α_1 - G_q → Phospholipase C – Phosphoinositides – IP_3, DAG- release of
Calcium
α_2 - G_i → ↓cAMP

Organ	Type of ®	Response
Radial Muscle (Iris)	α_1	Contraction-dilatation of pupil – Mydriasis
Heart	β_1	+ve Inotropic, +ve chronotopic ↓Enhance conduction Refractory period –Av Node
Arterioles – Skin Mucosa Abdominal Viscera	α_1	Vasoconstriction
Veins	α_1	Venoconstriction

Arterioles –skeletal Muscle	β_2	Vasodilatation
Lung – Tracheal, bronchial Muscle	β_2	Relaxation- Bronchodilation
Bronchial glands	α_1	↓Secretion
G.I.T	$\alpha_1, \alpha_2, \beta_2$	↓ Intestinal tone, Frequency & amplitude of spon contraction reduced.
sphincters -	α_1	Contraction
Urinary bladder	β_2	detrusor Relaxation
	α_1 -	Triagone Contraction
Uterus	β_2	Relaxation
Kidney –Renin secret	β_1	↑Renin secretion

• Liver	β_2	**Glycogenolysis**
• Pancreas (insulin)	α_1	↓ **secretion**
• Fat cells	β_3	**Lipolysis TG –fatty acids**
		Lipase
• Presynaptic	α_2	↓ **NE Release**
	β	↑ **NE Release**
• Skeletal muscle	β_2	**Change in contractility**
		↑ **K^+ Uptake.**

• Receptor	Agonist
α_1 β_1 β_2	Adrenaline
α_1 β_1 ; **no** β_2	Norepinephrine
α_1 β_1 D_1 D_2	Dopamine
D_1	Fenoldopam
α_1 **- Selective**	Phenylephrine, Mephenteramine
α_2 **- Selective**	Clonidine
β_{1-} **- Selective**	Dobutamine
β_{2-} **- Selective**	Salbutamol

Classification

- Chemical classification

Catecholamines

Non-catecholamines

- Depending on mode of action

Directly acting

NE, adrenaline, dopamine, salbutamol.

Indirectly acting

Tyramine

Mixed action

Ephedrine

Amphetamine

Vasopressors

NE, dopamine ,mephenteramine

Cardiac stimulants

Adrenaline, Dopamine, Dobutamine

Bronchodilators

Salbutamol, Salmeterol

Nasal decongestants

Phenylephrine, Xylometazoline

Uterine relaxants

Ritodrine, Isoxsuprine

Epinephrine / Adrenaline

- Catecholamine
- Adrenal medulla
- Receptors –α & β
- Actions :- Eye

  Mydriasis,↓ I.O.P

  - Heart
  - Blood vessels
  - B.P. – Systolic
    - Diastolic
    - Biphasic response
    - Dale's vasomotor reversal
  - Bronchial Muscle- Relaxation
  - Bronchial glands -↓ secretion
  - Mast cell (β2) -↓ Release of autacoids
  - G.T.T
  - Uterus
  - Metabolic

Uses

- **Anaphylactic shock**
- **Bronchial asthma**
- **Cardiac resuscitation**
- **Control of bleeding –Epistaxis**
- **With Local anesthetic**
- Dipivefrine-Highly lipid soluble-good penetration-Glaucoma

A/E

- **↑ B.P –Subarachnoid hemorrhage**
- **Ventricular fibrillation**
- **Tremors, palpitations**
- **Precipitate Angina**

Dopamine

Catecholamine

Receptors – α_1, β_1, Dopamine receptors.

At a dose- < 5 micrograms/ kg /min –D_1 receptors

Renal vasodilatation, Natriuretic

5-10 micrograms /kg /min –D_1receptors

β_1, - heart

10-20 micrograms /kg/min - β_1, receptors

> 20 micrograms /kg/min - α_1 receptors

Uses - oliguria

Heart failure

cardiogenic shock

Dobutamine

Mainly acts on β_1 receptors

Increases cardiac output.

No increase in heart rate.

Less increase in O_2 demand of heart as compared to dopamine.

Nor-adrenaline- used in shock in ICU

Doxidopa- prodrug –converted to NA, used in chronic orthostatic hypotension

Dopexamine- $\alpha_{1,}$ $D_{1,}$ β_2 receptors, CCF

Mirabegron- β_3 receptors

- **Ephedrine**

- Noncatecholamine
- Direct + indirect action
  release of NE from nerve terminals
  Tachyphylaxis
- Receptors α and β
- Penetrates BBB
- Resistant to MAO, COMT.
- Uses – Chronic bronchial asthma
  Nasal decongestant
  Hypotension following spinal anesthesia

Lacks selectivity and efficacy low

Selective α_1 stimulants

Mephenteramine	phenylephrine
Hypotension following Spinal anesthesia	As mydriatic –Fundoscopy Nasal decongestant

- **Selective β_2 stimulants**

Salbutamol
Terbutaline
Isoxsuprine

- **Uses – Bronchial asthma**
- **Uterine relaxant –Preterm labour**

β_2 agonist in bronchial asthma

1) Bronchodilation - β_2 receptor
2) Stabilize mast cells - β_2 receptor
3) Enhance mucociliary clearance
4) Resistant to MAO, COMT
5) Longer duration of action

Salbutamol
2mg, 4 mg tabs
Inhaler -100mg metered dose
Respiratory solution

Terbutaline
2.5, 5 mg tabs
Inj -0.5 mg/ml
Inhaler

- **Side –effects**

1) **Muscle tremors –Tolerance develops**
2) **Palpitations, tachycardia**
3) **Long-term use –diminished effectiveness**
   Down regulation of receptors

Chronic asthma

Acute attack of asthma

Status asthmaticus.

Nasal decongestants

Oral	Topical
Pseudoephedrine	Xylometazoline
Phenylephrine	Oxymetazoline
	Naphazoline

α_1 adrenergic agonist

1) α_1 ® present on blood vessels supplying nasal mucosa – constrict vessels.

decrease blood supply ---- ↓congestion of mucosa
shrinkage of swollen turbinates

2) α_2 By facilitating release of NE

Increase nasal patency

Lower nasal resistance

Subjective relief of nasal symptoms.

Uses

- Common cold
- Allergic rhinitis
- Acute otitis media
- Sinusitis
- To visualize nasal, nasopharyngeal mucus memb.

S/E

Oral –Insomnia

Topical-stinging sensation

After congestion

Long term use- Loss of efficacy, Damage to nasal cilia, Atrophic rhinitis, Anosmia

- **Amphetamine –Not used**

- **Noncatechoamine**
- **Direct + Indirect action**
- **Abuse liability –CNS effects, ↑ attention span**
  Decreases appetite

	Adrenaline	Noradrenaline	Dopamine
Endogenous	+	+	+
Site	Adrenal Medulla	Adrenergic nerve endings	CNS- Neurotra-nsmitter Basal ganglia
	Catecholamine	Catecholamine	Catecholamine
Structure			
Amino group	CH_3	No CH_3	
Penetration Of BBB	-	-	-
Receptor	α_1 β	v_1 β_1	α_1 β_1
Action	Direct	Direct	Direct
Effects on organs.			
Eye	Mydriasis	Mydriasis	
Blood – vessels			
α_1	Contraction	Contraction	Contraction at dose > 20mg 1kg / min

	Adrenaline	Noradrenaline	Dopamine
B.V.Supplying SK. Muscle β_2	Vasodilatation	-	-
P.R.	No. change/		at dose > 20 mg 1kg /min D1- Renal
Dopamine ®			cerebral Mesentreic Vasodilatation
Heart Intropic	+	+	+
H.R.	↑	↓	
C.O	↑	Unchanged or ed	↑
B.P Systolic			
Diastolic	No/ ↓	↑	
Bronchial Muscle β_2	Bronchodilation	-	-

	Adrenaline	Noradrenaline	Dopamine
G.I.T	Peristalsis	Peristalsis	-
Urinary bladder (β2)	Detrusor relaxtion	-	-
Uterus	Relaxation	-	-
Renin Secretion(β1)			
Liver β2	Glycogenolysis	+/-	
Lipolysis β3	Lipolysis	+	
Metabolism	MAO, COMT	Uptake I MAO, COMT	MAO, COMT
A/E		Extravasation Necrosis	
Onset	Fast	Fast	Fast
Duration	Short	Short	Short

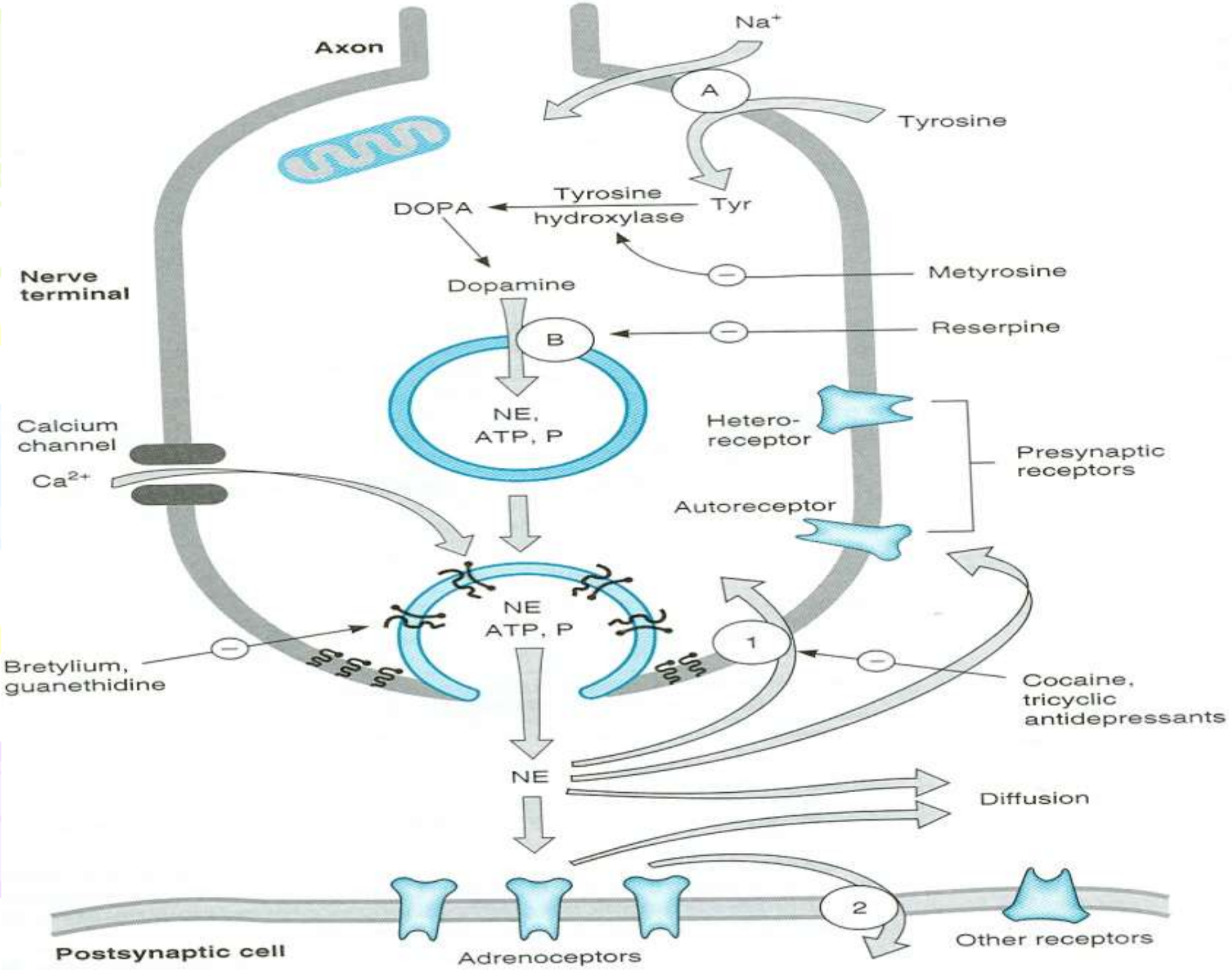
	Adrenaline	Noradrenaline	Dopamine
Uses		of shock –To T.B.P-Not responding to dopamine	olig urio Heart failure Cardiogenic shock endotoxic shock
Route	i.m S/C	i./v infusion 5% Dectrose	i.v infusion - < 5 mg 1kg / min D_1® - 5-10 mg 1kg / min D_1® β_1 ® - 10-20mg 1kg / min β_1 ® -> 20mg 1kg / min α ®

	Ephedrine	Mephentreramine	Phenylephrine
	Noncatechol	**Noncatecholamine**	**Noncatecholamine**
Benzene ring With OH at Passition 3 and 4	**-**	**-**	**3 OH.**
Receptor	**α_1 β_1 α_1**		**α_1**
Action	**Direct Indirect -by Releasing NE From never terminals**	**Direct +Indirect**	**Direct**
Penetration of BBB	+	+	+
Actions Eye			**Mydriasis**

	Ephedrine	Mephentreramine	Phenylephrine
Blood vessels	Contraction	Contraction	Contraction
P.R.	↑	↑	↑
Heart Intropic	+	+	-
H.R.	↑	↓	↓
B.P Systolic	↑	↑	↑
Diastolic	↑	↑	↑
Bronchial Muscle β_2	Bronchodilation	-	-

	Ephedrine	Mephentreramine	Phenylephrine
G.I.T	Peristalsis		
Urinary bladder (β2)	Detrusor relaxtion	-	-
Uterus	Relaxation	-	-
Renin Secretion(β1)			
Liver β2	Glycogenolysis		
Fat cell lipolysis	+		
Metabolism MAO, COMT	Resistant	Resistant	Resistant
A/E	CNS stimulation Insomnia		
Onset	Slow	Prompt	Prompt
Duration	Long	Long	Long

	Ephedrine	Mephentreramine	Phenylephrine
Uses	**Chronic-bronchial asthma, Hypotension**	**Of hypotension after spinal anes**	**-Mydriatic -Nasal decongestant -PAT**
Route	**Oral**	**i.m Oral**	**S/C i.m i.v, local oral**
Tachyphylaxis	**++**		


Axon
Na+
A
Tyrosine
Tyrosine hydroxylase
Tyr
DOPA
Dopamine
Metyrosine
Nerve terminal
B
Reserpine
NE, ATP, P
Calcium channel
Ca2+
Hetero-receptor
Presynaptic receptors
Autoreceptor
NE ATP, P
1
Bretylium, guanethidine
Cocaine, tricyclic antidepressants
NE
Diffusion
2
Other receptors
Postsynaptic cell
Adrenoceptors