NEUROTRANSMITTER

- ***Neurotransmitter is a type of chemical messenger that transmits signals across a chemical synapse, from one neuron to another.***

- ***sympathetic= adrenergic***
- ***Para-sympathetic= cholinergic*** (Neuron)

DEPTH OF BIOLOGY

- Both adrenergic and cholinergic division work antagonistically to maintain homeostasis
- Adrenergic system produces catecholamines like dopamine, epinephrine, non-epinephrine

DEPTH OF BIOLOGY

DOPAMINE [PLEASURE]

DEPTH OF BIOLOGY

Dopamine is responsible for allowing you to feel pleasure, satisfaction and motivation. When you feel good that you have achieved something, it's because you have a surge of dopamine in the brain.

EPINEPHRINE [ADRENALINE]

It is produced in stressful or emergency situation. Increase the heart rate and flow of blood, leading to physical boost and heightened awareness

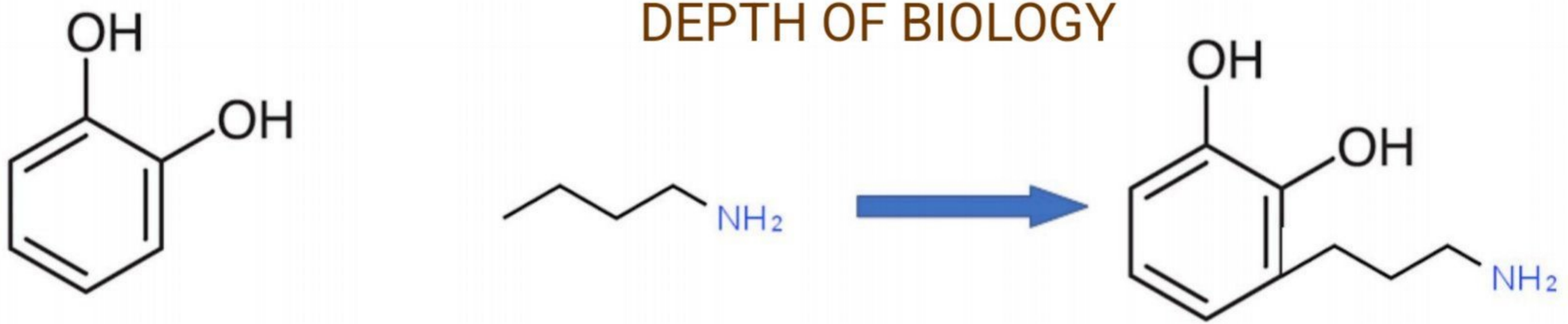
NOR-EPINEPHRINE [NOR-ADRENALINE]

Affects the response and attention action of brain . Increasing the blood flow and contracting the vessels

DEPTH OF BIOLOGY

CATECHOLAMINES

- A catecholamine is a monoamine neurotransmitter, that has a catechol ring and a side-chain amine.



BIOSYNTHESIS OF CATECHOLAMINES

- It takes place in dopaminergic and adrenergic neurons in the CNS, in the sympathetic neurons, ANS and in adrenal medulla

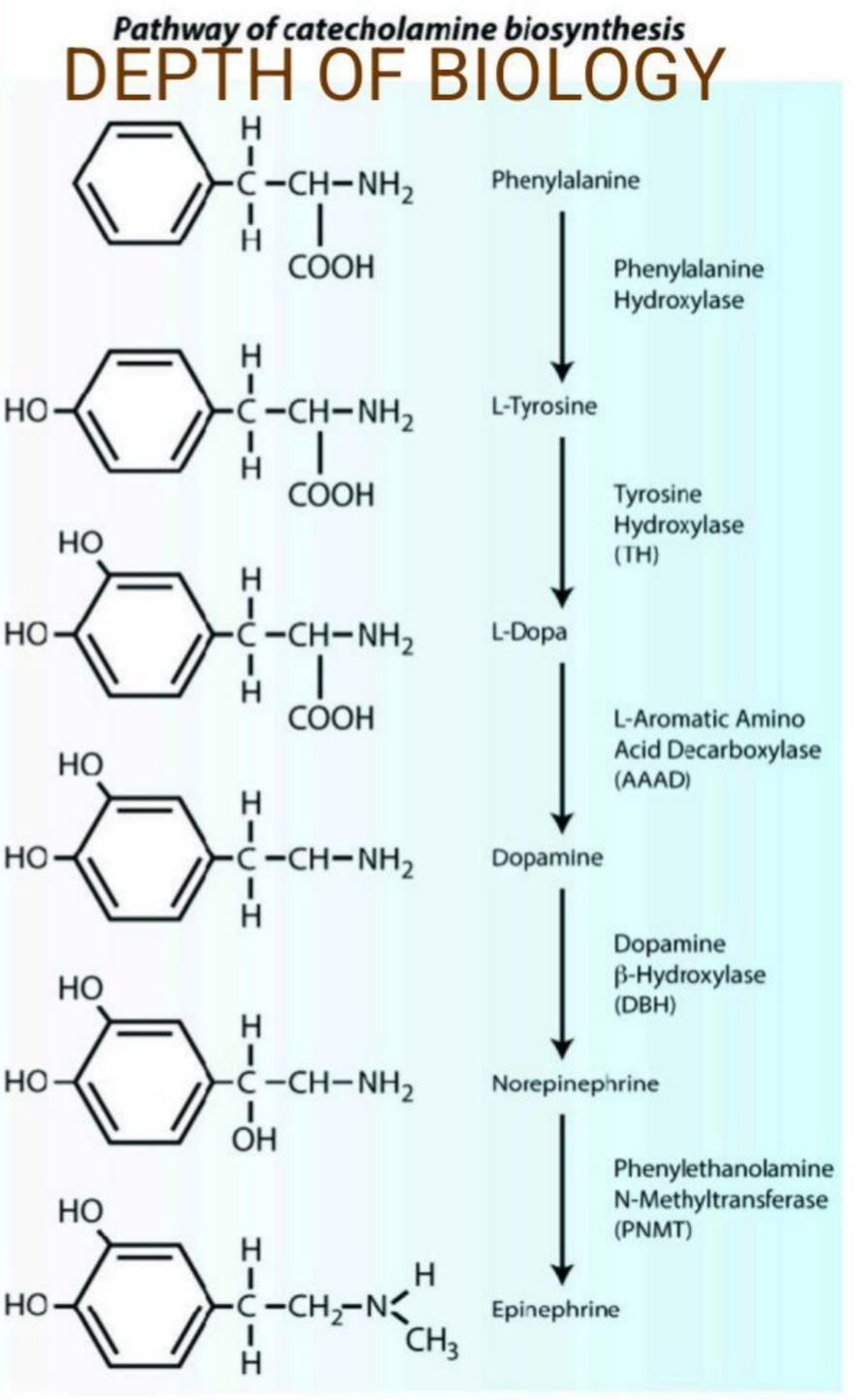
  Phenylalanine gets hydrolyzed into tyrosine in liver.

  Tyrosine hydrolyzed to DOPA by the enzyme tyrosine hydroxylase [in cytoplasm of neuron].

  DOPA is converted into dopamine with help of DOPA carboxylase [in cytoplasm of neuron].

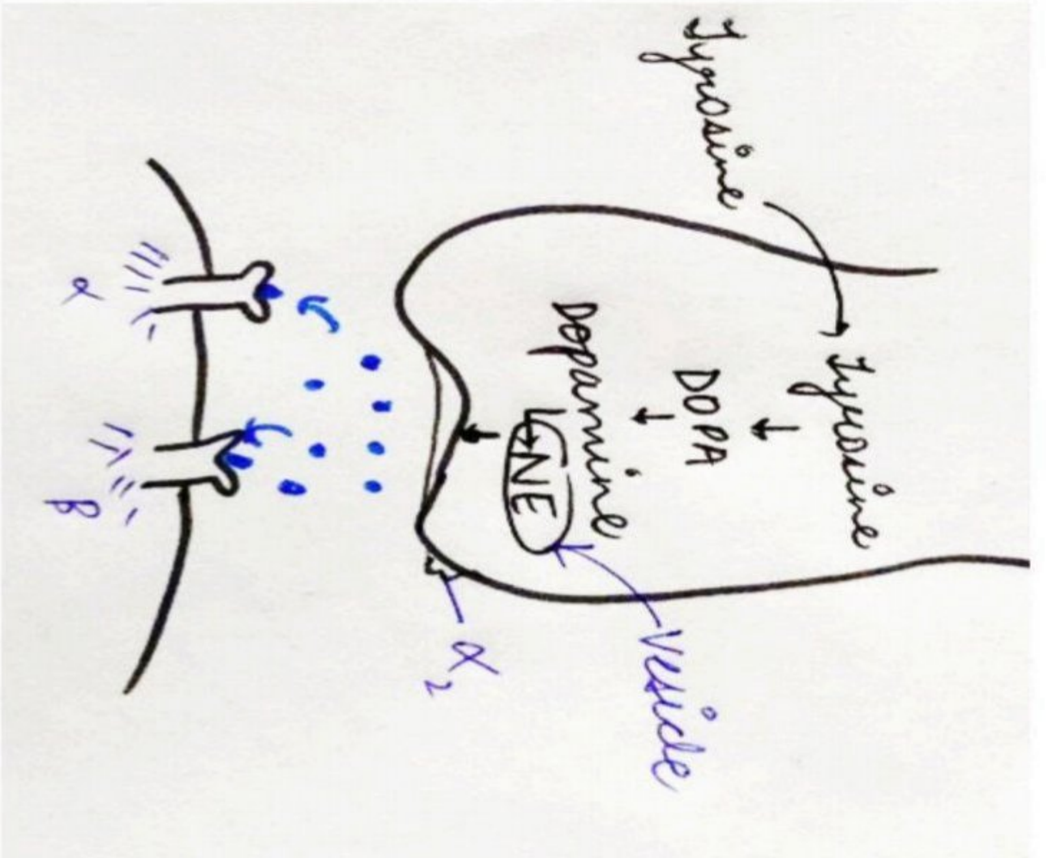
  Dopamine is converted to non-adrenaline with help of dopamine **β** hydroxylase

DEPTH OF BIOLOGY



SYNTHESIS & RELEASE OF NEUROTRANSMITTER

- Nor-adrenaline formed in nerved ending remain stored in vesicles in the form of ATP complex. DEPTH OF BIOLOGY
- Nor-adrenaline gets diffused out in cytoplasm and gets methylated into adrenaline
- Adrenaline enters the chromatin granules and gets stored DEPTH OF BIOLOGY
- Now, neurotransmitter is released from vessels
- Then neurotransmitter bind with receptor and give response



DEPTH OF BIOLOGY

CATABOLISM OF CATEHCOLAMINES

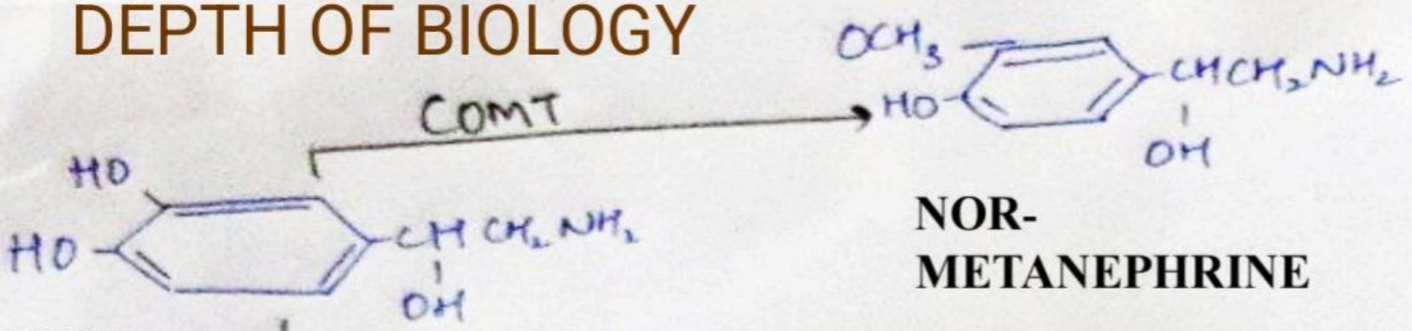
- It is removal of catecholamine and termination of action of catecholamine
- In this process, structure of catecholamine change with the help of enzymes [MAO, COMT]. DEPTH OF BIOLOGY
- So they do not react with adrenergic receptor to produce effect.

DEPTH OF BIOLOGY

MAO= monoamine oxidase [deamination]

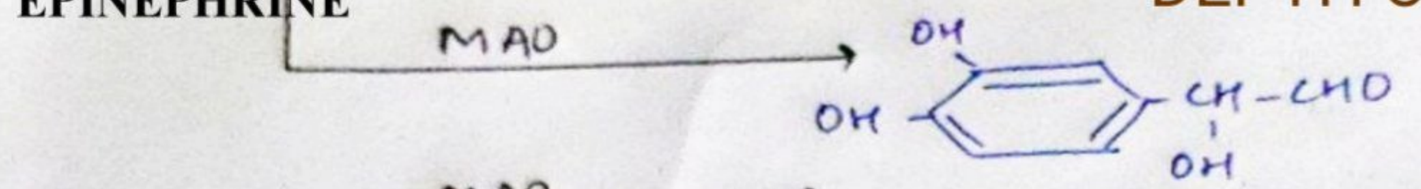
COMT= catechol O-methyl transferase [methylation in ring]

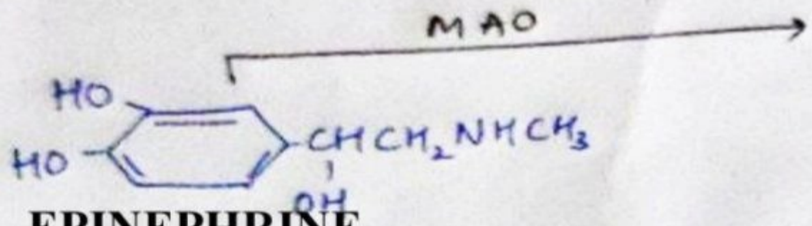
DEPTH OF BIOLOGY



NOR-EPINEPHRINE

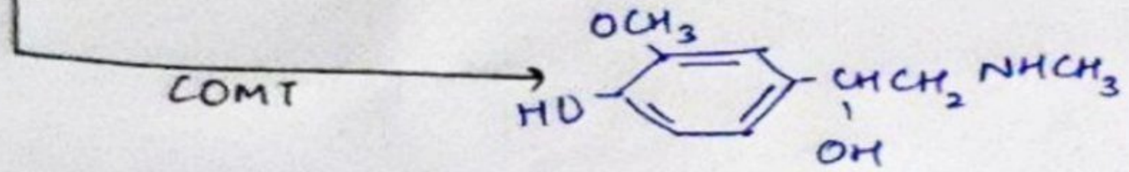
NOR-METANEPHRINE





3,4 DIHYDROXY-PHENYLGLYCOALDEHYDE

EPINEPHRINE



METANEPHRINE

ADRENERGIC RECEPTOR AND THEIR DISTRIBUTION

- Those receptors in which adrenergic drugs/ neurotransmitter will directly bind to induce various action/responses
- Adrenergic receptor are membrane bound CH protein coupled receptors
- These are classified as

α- α1 and α2

β- β1, β2 and β3

DISTRIBUTION OF ADRENEGRIC RECEPTOR WITH THEIR ACTION

- **α1 RECEPTOR-**
- it is present on post synaptic receptor sites
- Smooth muscle of blood vessels [vasoconstriction]
- Gland cells [gland secretion]
- Glycogenolysis in liver [glucose synthesis]
- Also presents in iris of eye, bladder and uterus
- These are mainly excitatory in nature

- **α2-**
- Present on both pre and post synaptic receptor sites
- Inhibit neurotransmitter release

β1-

Present in cardiac tissue and kidney

Contraction of heart increases

Release renin from kidneys results increases blood pressure

Excitatory in nature

β2-

Present in smooth muscle and gland cell i.e bronchi, uterus, liver, GIT

Relaxation – vasodilation, relaxation, bronchodilation

Inhibitory in nature

β3-

Present in adipose tissue and urinary bladder

Function is lipolysis in adipose tissue and relaxation in urinary bladder

SYMPATHOMIMETIC AGENTS

- Sympatho – nervous system and mimetic = copying [mimic]
- Also known as adrenergic agents.

- Those agents which copy the action of sympathetic nervous system are known as SYMPATHOMIMETIC AGENTS

- These agents bind with adrenergic receptor and give action

SAR OF SYMPATHOMIMETIC AGENTS

SAR= structure activity relationship

- Relationship between chemical structure of a molecule and its biological activity

INDIRECT ACTING DRUGS

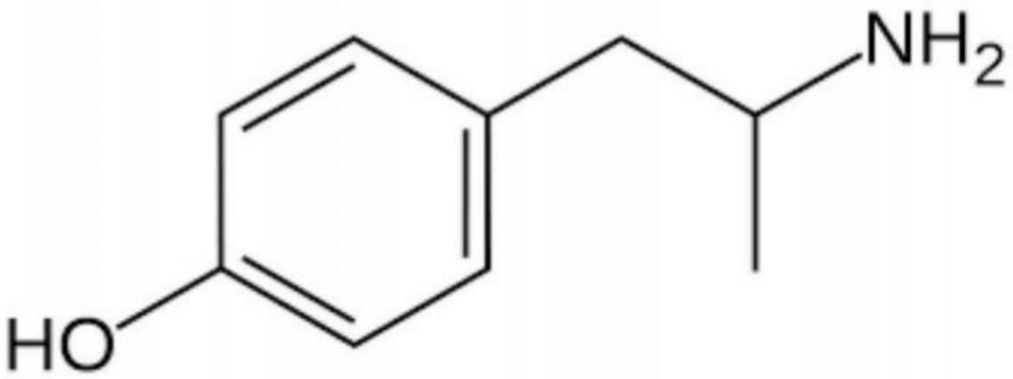
- Act indirectly to increase concentration of neurotransmitter by causing its release
- These drugs themselves do not react with the receptor but causes release of neurotransmitter from storage sites which then interact with receptor to produce effects.

1.HYDORXYAMPHETAMINE- white powder freely soluble in water

MECHANISM OF ACTION-

Cause release of nor-adrenaline from synapse

& cause dilation of pupil.



USES-

- Used as an eye drop to dilate pupil

AGENTS WITH MIXED MECHANISM

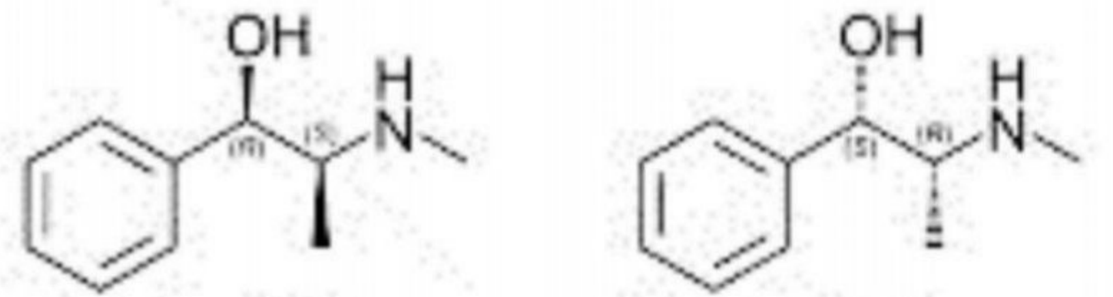
- These directly act on adrenergic receptor and also effect release of nor-adrenaline
- Act both ways- direct & indirect

1.EPIHEDRINE-

Occurs naturally in ephedra

2 asymmetric carbon; 4 optical

Isomers



(1*R*,2*S*)-(−)-Ephedrine (1*S*,2*R*)-(+)-Ephedrine

MECHANISM OF ACTION-

Stimulates CNS and both receptors [α& β]

ADRENERGIC ANTAGONISTS

- Those drugs which inhibit the effect of the sympathomimetic agents by blocking the receptors.

ANTAGONIST= oppose the agonist

- Alpha [α] adrenergic antagonist
- Beta [β]adrenergic antagonist .

Alpha [α] adrenergic antagonist- receptor which block the α- receptor and antagonizes the effect produced by the drugs acting on α- receptors.

Alpha adrenergic blockers

BETA β ADRENERGIC BLOCKERS

- Those drug which block β receptor and agonizes the effect produced by drugs.

DEPTH OF BIOLOGY

- These are mainly used as anti-hypertensive agents
- It can be classified as
  - β**1** selective
  - β**2** selective
  - Non selective [blocks β**1** and β**2**]

DEPTH OF BIOLOGY

➢ ***β1 selective-*** cardio selective β blockers drugs have affinity for only β**1** receptor which are present in the heart. So, blockers are mainly used in treatment of hypertension

DEPTH OF BIOLOGY

➢ ***β2 SELECTIVE-*** **β2** receptors are present in lungs and bronchial muscles. So **β2** blockers causes contraction of bronchial muscles

DEPTH OF BIOLOGY

➢ ***NON-SELECTIVE:*** Non- selective β blocker act on both β1 & β2 receptor, used in treatment of ocular hypertension and glaucoma.

➢ SAR OF β BLOCKERS

➢ PROPRANOL DIAG

DEPTH OF BIOLOGY

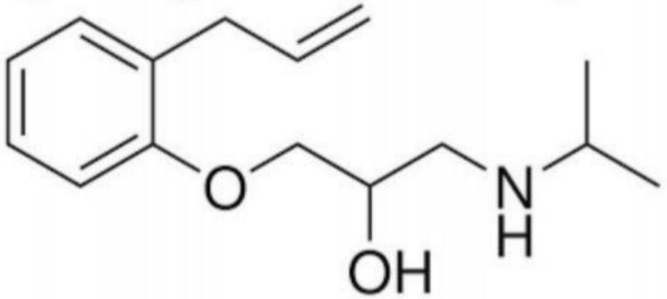
➢ Structurally, substitution is possible on-

- Aromatic ring
- Carbon chain
- Amino group

DEPTH OF BIOLOGY

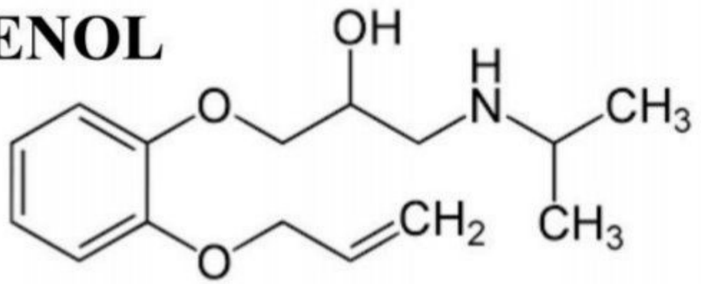
- AROMATIC RING- most of the derivatives have substituted phenyl ring in place pf naphthyl ring DEPTH OF BIOLOGY

Alkenyl & alkanyloxy group when present in ortho position on phenyl ring, give good β antagonist activity



ALPRENOL
OL

OXPRENOL
OL



Addition of –OH group in phenyl ring lead to removal of antagonist activity DEPTH OF BIOLOGY

If phenyl ring is replaced by naphthyl /substituted naphthyl , than they are non- selective

EG- propranolol: non- selective

Atenolol, betazold, bisoprolol etc: selective

DEPTH OF BIOLOGY

- ***CARBON CHAIN-*** the OCH2 group is placed between the aromatic ring and ethanol amino side chain, increase activity or essential for the activity [aryloxy propanolamine]
- If there are H in place of –OCH2 then compound is known as aryl ethanolamine [non-selective].

- ***AMINO GROUP-*** if isopropyl and t butyl group present on amino group then it provides nucleophilicity to the amino group (increase activity)

EG- atenolol and timolol.

NEUROTRANSMITTER

- *Neurotransmitter is a type of chemical messenger that transmits signals across a chemical synapse, from one neuron to another.*

- *sympathetic= adrenergic – [release adrenaline]*
- *Para-sympathetic= cholinergic - [release acetylcholine]*

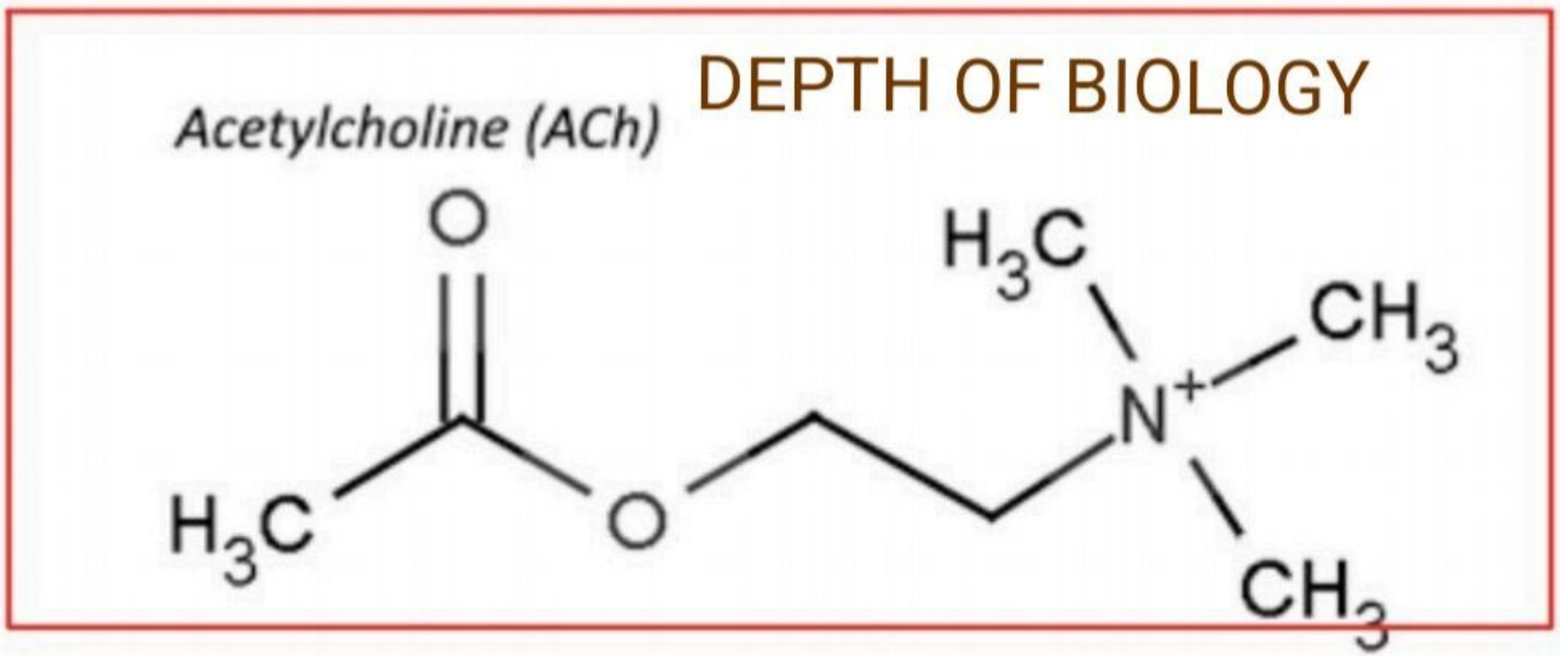
CHOLINERGIC NEUROTRANSMITTER

- Found or released from nerve ending of parasympathetic ending

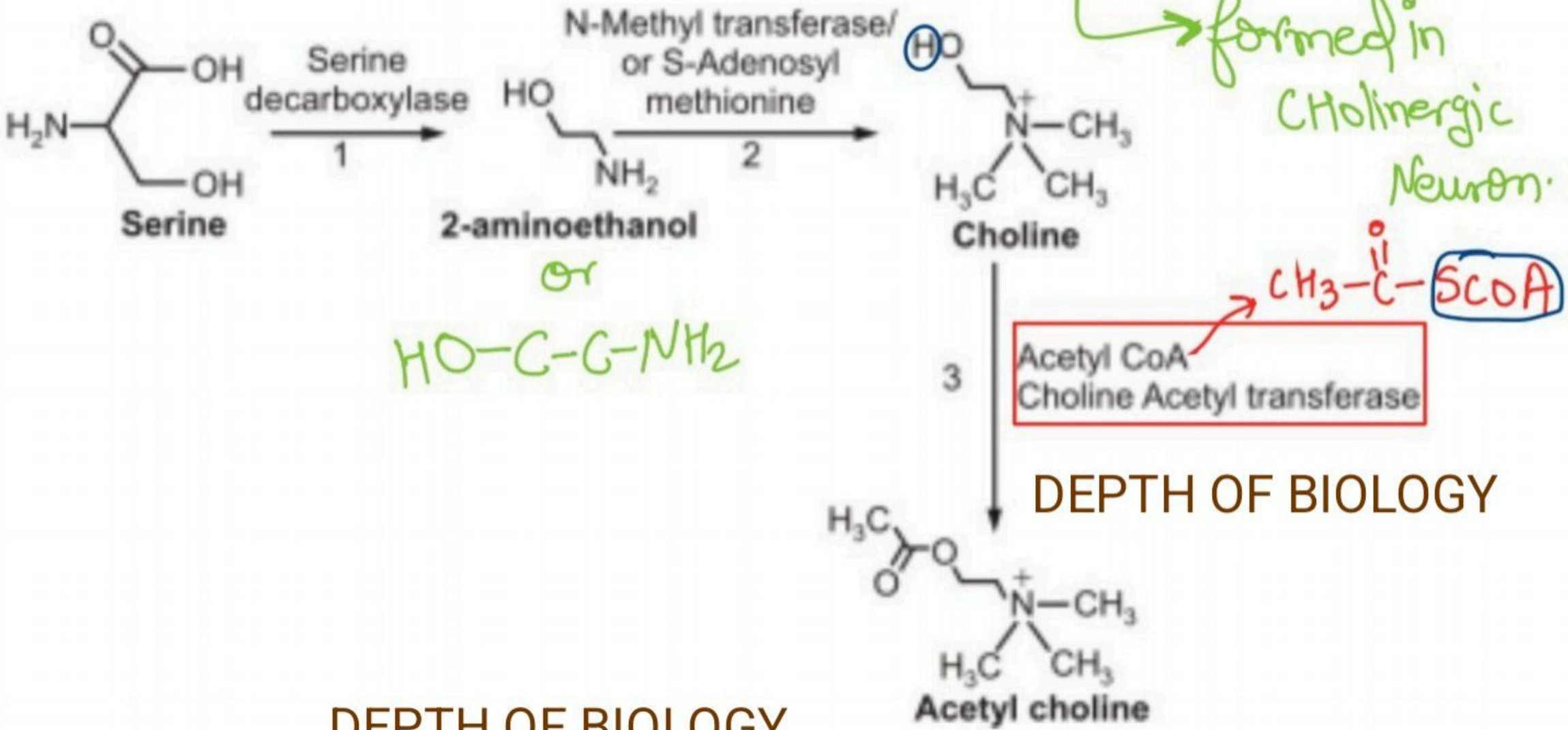
- ACETYLCHOLINE- (Ach)

Present at post ganglionic synapses of cholinergic /parasympathetic nerve ending

Major neurotransmitter



BIOSYNTHESIS , STORAGE & RELEASE OF ACHc (Acetylcholine).



formed in Cholinergic Neuron.

- *Acetylcholine* is synthesized by choline and acetyl coenzyme A with the help of enzyme *acetylcholintransferase.*
- Choline is synthesized by liver from reaction of serin and ethanolamine.

Serine + Ethanolamine ⇒ Choline.

Acetyl A Co-enzyme + Choline → Enzyme in Nerve ending → Acetylcholine

STORAGE

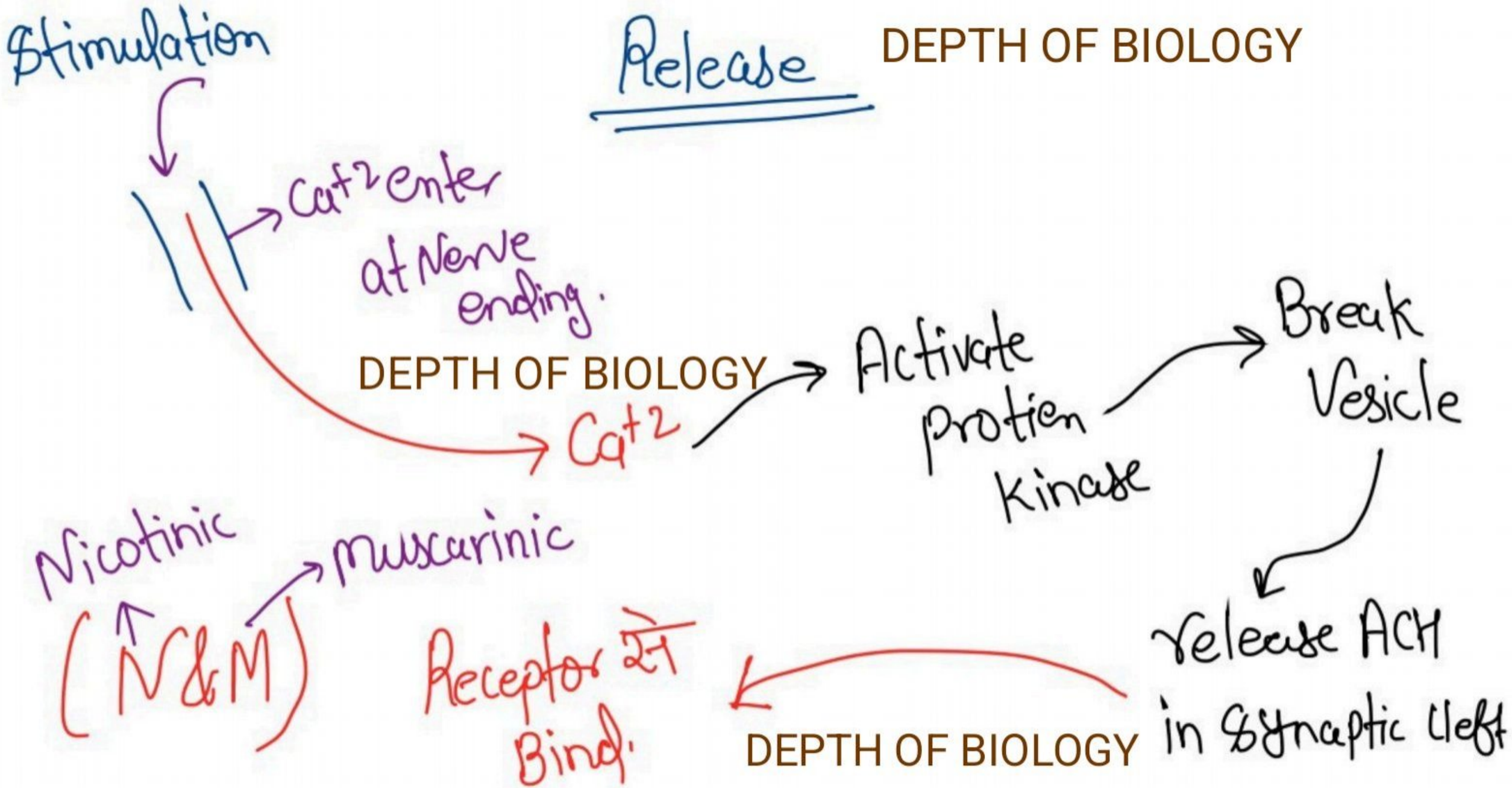
- Stored in storage vesicles by the vesicular Ach transporter (VAchT)
- Each vesicle contain about 1k-50k Ach molecules
- Protection from Ach is provided by the vesicles

Choline Transfer by Choline Transport System → reach Nerve ending.

In Nerve Ending.

Acetyl + Choline → (Acetylcholin Transferase) → Ach.

Release

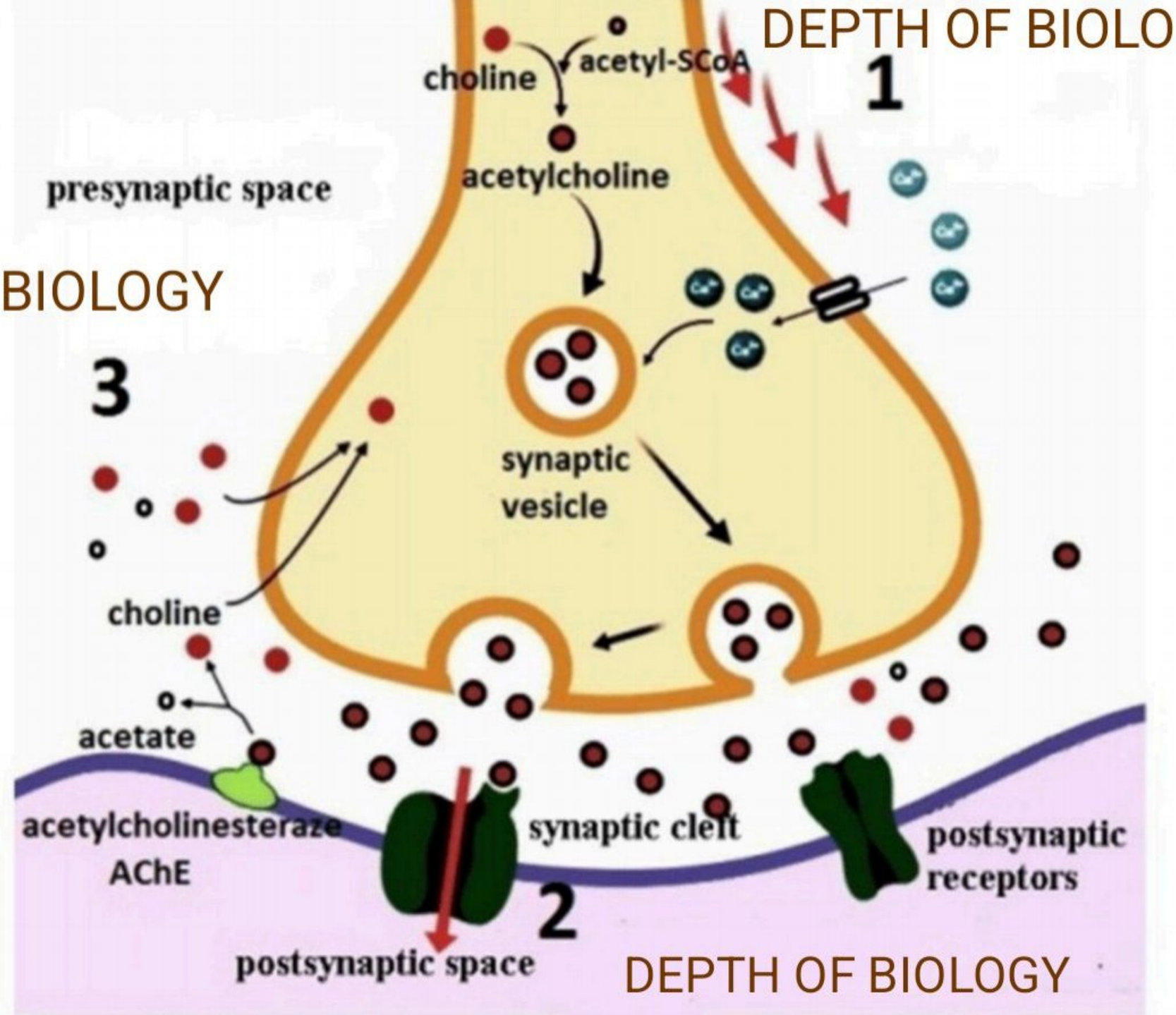


CATABOLISM OF ACETYLCHOLINE

- Cholinesterase`s enzyme also known as acetylcholine esterase`s (AchE) hydrolyses acetylcholine (Ach) into the inactive metabolite choline and acetic acid

ACETYLCHOLINE $\xrightarrow[\text{Cholinesterase}]{\text{Hydrolysis}}$ CHOLINE + ACETIC ACID

Botulinum toxin inhibit Ach release



CHOLINERGIC RECEPTOR & THEIR DISTRIBUTION

- Cholinergic neurotransmitter directly bind to induce various response

- Classified into 2 types-

MUSCARINIC [M]

- M1
- M2
- M3
- M4
- M5

NICTONIC [N]

- NM
- NN

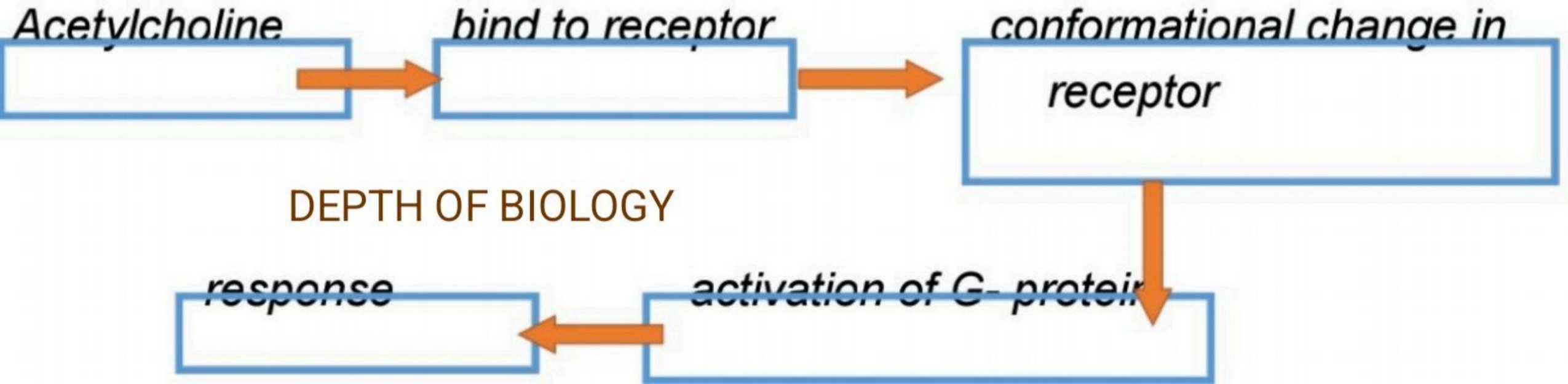
MUSCARINIC [M] RECEPTORS

- Muscarinic receptors are G-coupled protein receptors involved in the parasympathetic nervous system.

- Muscarine is a water soluble toxin derived from mushroom *amantia muscaria* ; it causes activation of PNS → plant

→ HR↓ (Body Normal).

- *Mechanism-*



① M_1 → ⊕nt in CNS & Gastric Gland.

→ Release → Histamine

→ Acid Secretion. (Affect memory, Learning, function)

② M_2 → ⊕ntin Heart.

→ ↓se Conduction of Heart.

H.R↓

Eg- Ach, methacholine, bethanechol etc are some drugs which bind with M receptor

③ M_3 → ⊕nt in Smooth muscle of Blood vessle & in lungs.

function → Cause Contraction of Smooth muscle.
(Broncho Constriction).

→ Nitrooxide release (Vasodilation).

M_4 ⇒ ⊕nt in CNS & Heart.

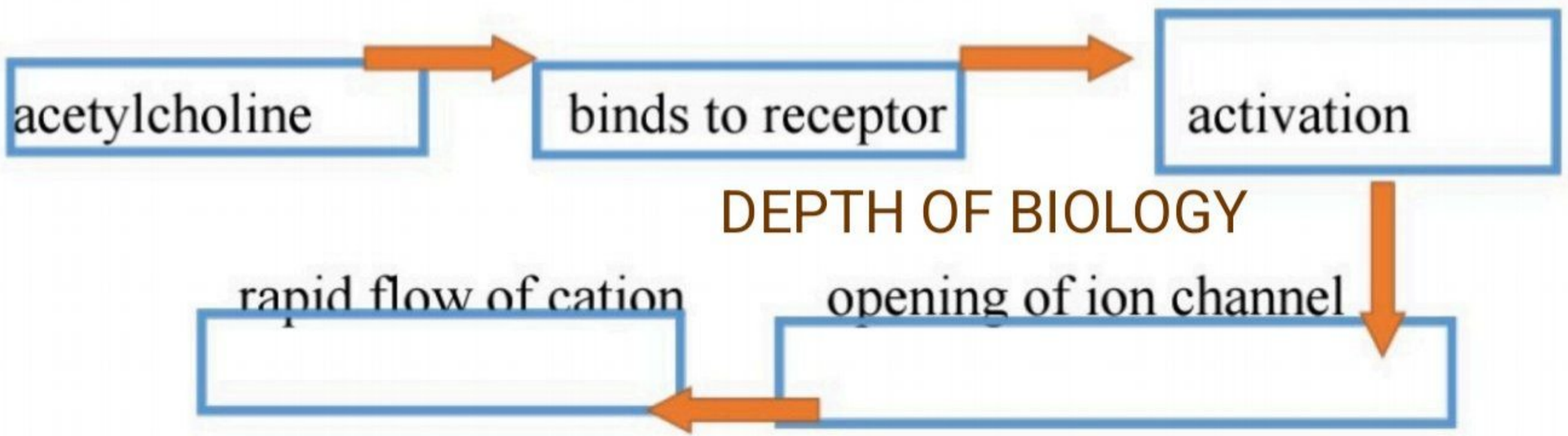
→ Inhibit ACH release

M_5 → ⊕nt in CNS

→ Dopamine release

NICTONIC [N] RECEPTORS

- Ionotropic receptor → Ion Channel open.
- NICTONIC- stimulates the pleasure center of brain [a highly addictive drug]
- MECHANISM-



① N_m → Present in Skeletal muscle.

↳ Skeletal Muscle Contraction.

N_m = Muscle type Nicotinic receptor

⇒ ↑se Cation permeability (Na^+ & K^+).

eg → Phenyl trimethyl.

② N_n ⇒ (Neuronal type Nicotinic ®) ⇒ Present

↳ function → Depolarisation

→ Secrete Catecholamines.

Present → Adrenal medulla.

→ Spinal cord.

→ Brain