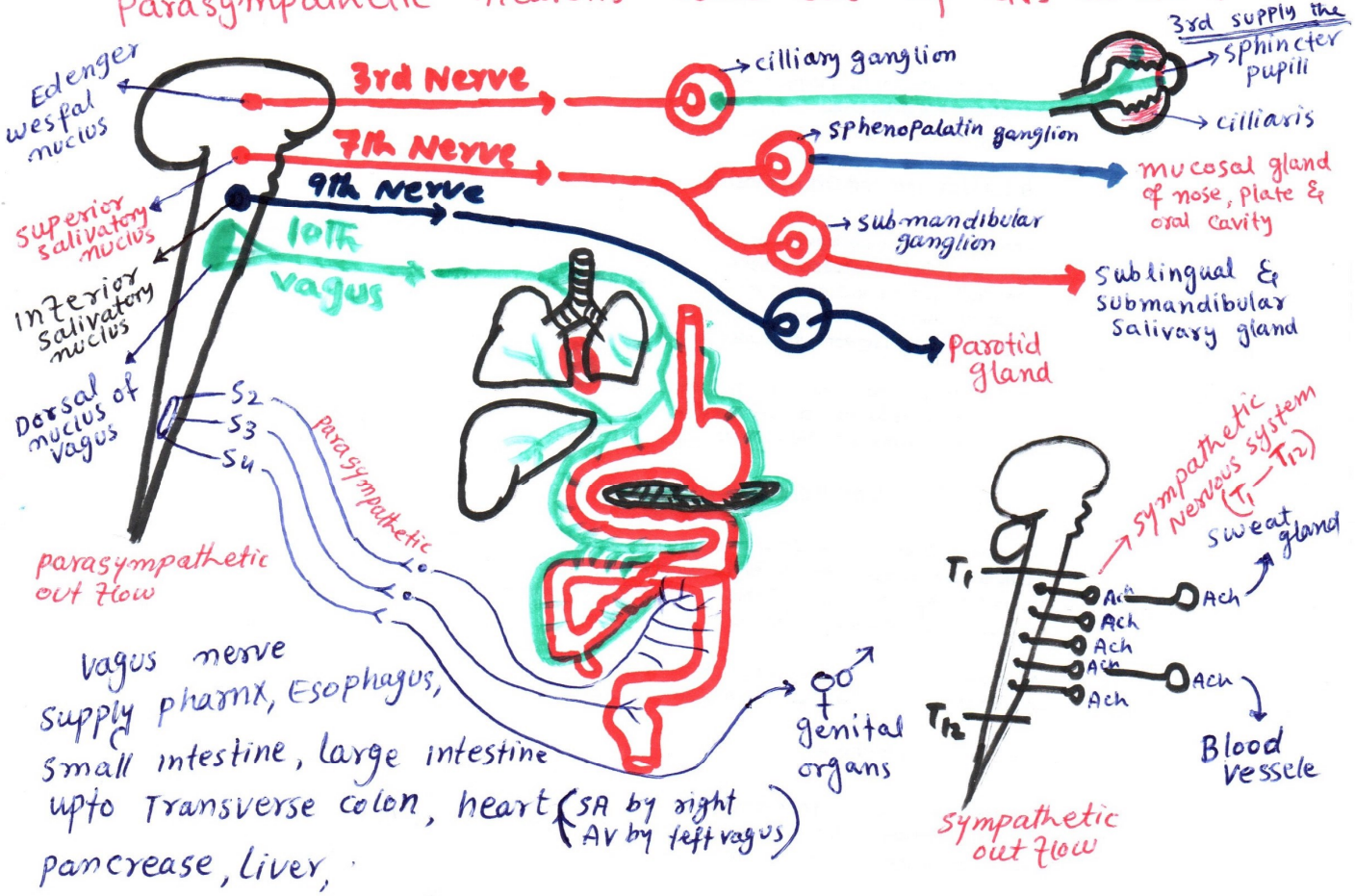
Cholinergic system

By: Zakirullah Yousufzai

All neurons which release Acetylcholine as a neurotransmitter are called Cholinergic neurons.

Cholinergic system is related with sympathetic & parasympathic neurons outflow

Parasympathetic neurons come out of CNS at specific points.



cholinergic preganglionic + postganglionic neuron both secret Acetylcholin

All Preganglionic sympathetic neurons are cholinergic, while post ganglionic are adrenergic but some exception:

① Post ganglionic sympathetic which innervate Blood vesseles → which releas Ach

② Post ganglionic sympathetic which supply sweat glands. also release Acetyl cholin

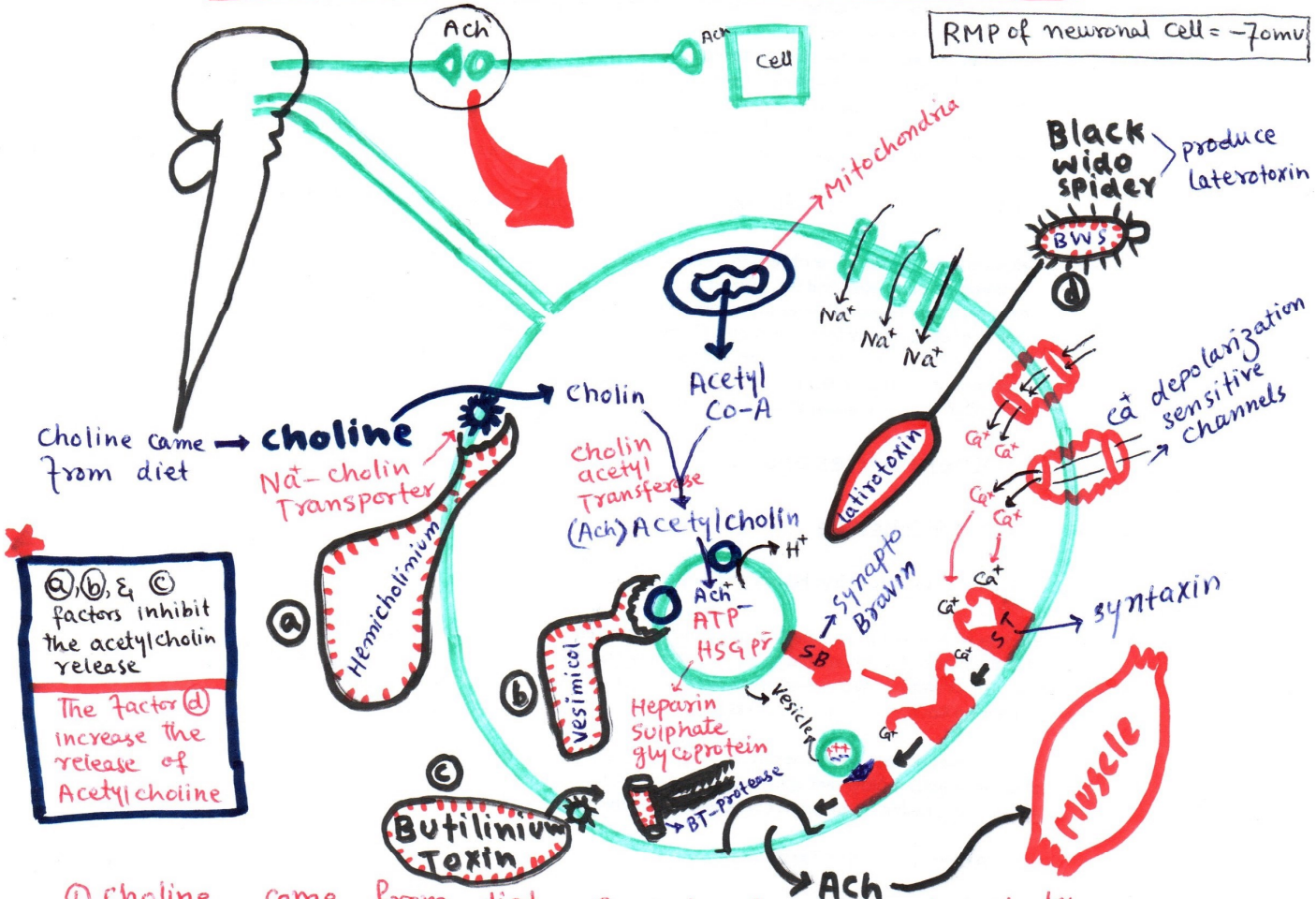
All the neurotransmitter which are peptide (larger molecular weight) are synthesized in cell body.

All the neurotransmitters which are small molecular weight are synthesized in nerve ending.

nerve ending are specilized structure which can synthesize, store, & release small amount neurotransmitter.

e.g Acetyl cholin, Nor Epinephrin, Epinephrin, histamin, serotonin.

How Acetyl cholin are synthesized



① Choline come from diet, & enter to neuronal end by Na^+ – cholin Transporter, choline are abundant Extracellecularly.

② Acetyl CoA released from mitochondria

③ cholin & Acetyl Co-A are combined by Choline-acetyl Transferase & make Acetyl Cholin, which enter to vesicle by Ach – H^+ Antiport, within the vesicle HSG Pr^- are -ve & Ach are +ve so attract oneanother ATP within the vesicle are also -ve charged so attract more Ach.

④ during Action potential when Na^+ come into cell, the cell become depolarized than Ca^+ depolarize sensitive channel opens & alot of Ca^+ come & bind with syntaxin, due to which the mouth of syntaxin opens & bind with SB than the vesicle touch with membrane & release Acetylcholine.

Factors which interfer with Acetyl Coline Release

(a) Hemicholinium acts on cholinergic nerves at Na^+ – choline Transporter, & block the transporter, so no choline enter inside

(b) Vesimicol inhibit Acetylcholine – proton ($Ach-H^+$) Antiport, so thus Acetylcholin can't enter to vesicle, for storage.

(c) Butilinium Toxin will cause paralysis of Muscle by decreasing the release of acetylcholine at cholinergic nerve ending

cholinergic nerve ending which are at neuromuscular junction have special transporters which transport Butilinium Toxin inward.

Butilinium Toxin have an enzyme (Butilinium protease) which can break down the synaptobravin & syntaxin proteins, so than vesicle can't fuse with membrane so, Acetylcholine is there but not released, at neuromuscular junction, so no muscle contraction occur, leading to paralysis of Muscles.

(d) Black wido spider produce a toxin called **Laterotoxin**

laterotoxin increase interaction B/w synaptobravin & syntaxin & with also other proteins, so when these proteins ~~act strongly~~ interact strongly large amount of ~~Protein~~ acetylcholin is released, so acetylcholine crisis occur; There will be Lacrimation, Salivation, Bradycardia abdominal cramps, defication & Micturation ------ etc

choline Can't cross BBB, How It reaches to CNS?

In Perephral part of the body cholin join a protein Called Phosphatidyl choline, than this Phosphatidyl choline enter into CNS, & break down into choline

cholinergic nerve ending are very active metabolically

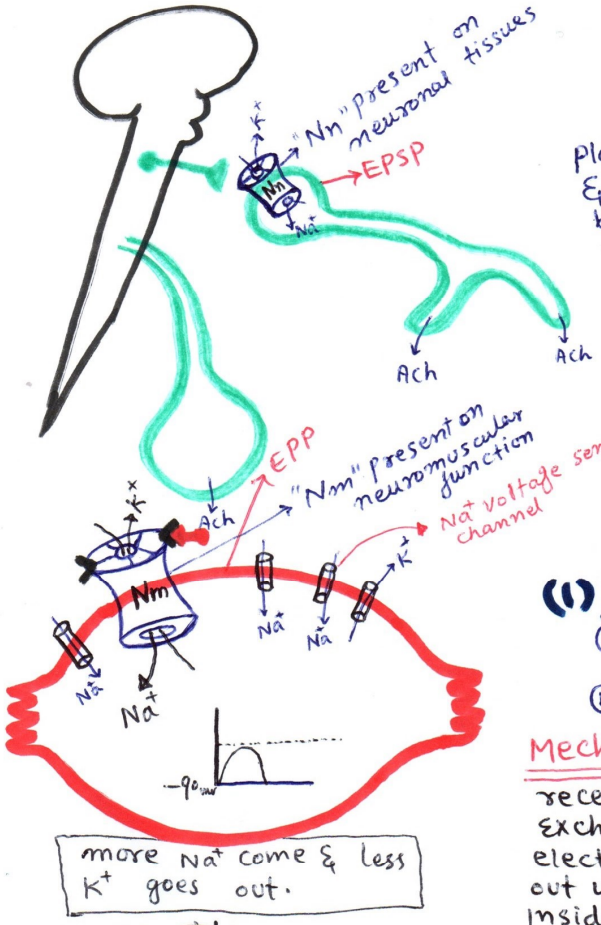
* Acetylcholine are released in small amount all the time at neuromuscular junction
* large amount release when action potential occur

⇒ action potential is a wave of depolarization followed by wave of repolarization.

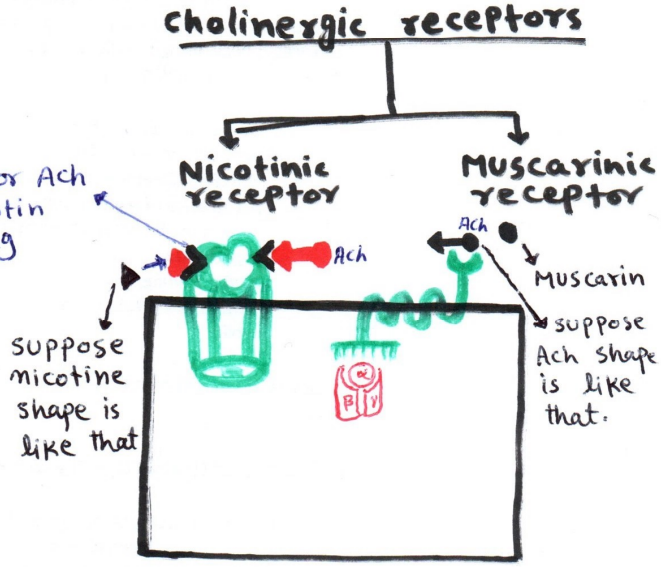
Example
Small amount release is like warmup & large amount release is like full exercise

Conduction	Transmission
movement of impulse along the muscle or nerve endings	when information pass from one nerve ending to another membrane. ie Impulses moving from presynaptic membrane to post synaptic membrane

How Acetyl choline works



more Na^+ come & less K^+ goes out.



(1) Nicotinic Cholinergic receptor

ⓐ To this receptor Nicotin & Acetylcholine both can bind
ⓑ All nicotinic channels are Ion channel

Mechanism of action: Nicotine/Ach bind with receptor, the receptor opens & Monocatonic exchange take place, Na^+ move inward against electro +ve concentration gradiant & K^+ move out ward against concentration gradient, so inside electro negativity les & cell go to +ve side. ie: Excitation of cell take place.

(2) Muscarinic Chol·R:

these are G-protein coupled 7-pass receptor, Stimulated by Ach & Muscarine.

Mechanism of action at neuromuscular junction

- Na^+ move in through Ion channel (Nicotinic receptor), if small amount Na^+ move in, it will not ↑es potential more from RMP (Resting membrane potential), But if large amount of Ach act on receptor, large amount of Na^+ move in ↑es potential from RMP.

[**Threshold**: Voltage at which voltage gated Na^+ channels opens.]

They will carry voltage from RMP to EPP (End plate potential)

If EPP is greater enough to reach to threshold, than large Nomber of Na^+ channel Opens & Na^+ move in, so potential ↑es upto action potential & action potential take place, cell become depolarized, such cell open K^+ channel and K^+ rush out, again inside electronegativity ↑es & cell become repolarized

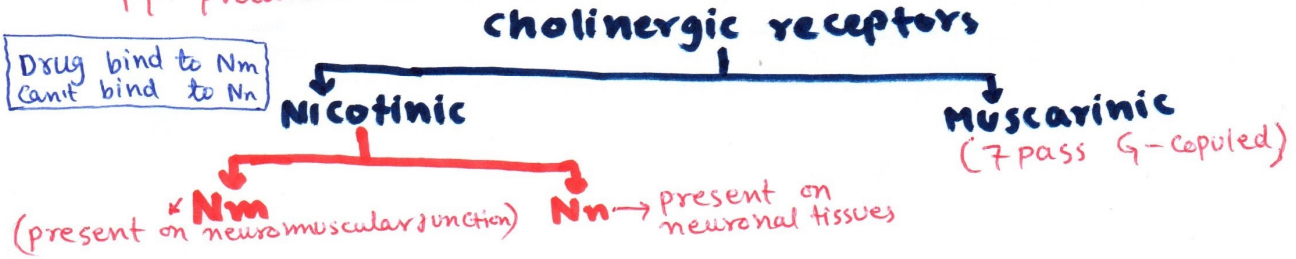
On this way wave of depolarization move on muscle membrane.

this receptor on muscle membrane is Called Nm (Nicotinic receptor on muscle end plate)

- Another way of nicotinic receptor action on post synaptic neuronal membrane.

presynaptic → Ach → Nicotinic receptor on postsynaptic membrane → Na^+ move in Post synaptic membrane & ↑es potential from RMP to EPSP (Excitatory post synaptic potential)

EPP & EPSP are same, if Produced on neuromuscular Junction is Called EPP,
If produced on nerve membrane is Called EPSP.



Stimulation of Nm

- **Ach**
- **Nicotine**
- **Succinyl choline**

If Ach bind to this receptor, it will allow this receptor to allow Little Na^+ to move in after that receptor will be automatically blocked.
If we want this receptor to stimulate again Ach should be removed & than bind again, but the old Ach is destroyed by Acetylcholine Esterase, which is present abundantly on post synaptic membrane.

Acetylcholine $\xrightarrow{\text{Acetyl cholin esterase}}$ **Acetyl Co-A + Choline**

Initially these receptors are stimulated & than Desensitized.

Succinyl Choline is used as paralysing agent, it is actually used to stimulate the receptor but, its over stimulation cause inhibition of further stimulation, so no further contraction occur.

There is no enzyme at receptor to destroy Succinyl cholin, so it cause over stimulation & eventually desensitization of receptor.

Tubocurarin:

tubocurarin block Nm, this drug bind & block Acetylcholin receptor on neuromuscular cholinergic receptor

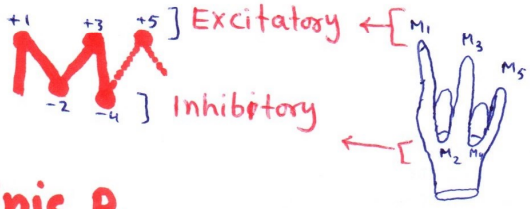
Drugs which block Nn

1. Mecamylomine
2. Trimethopan
3. Bungarotoxin

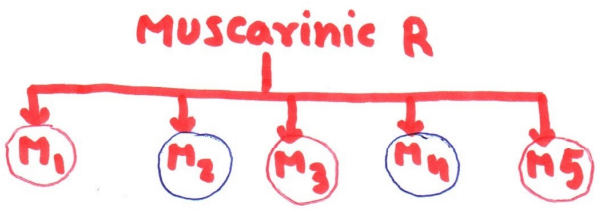
Cholinergic pathway in CNS are concerned with learning & memory.

Muscarinic Receptors

Muscarinic receptors are present on those tissues which are innervated by parasympathetic post ganglionic neurons.



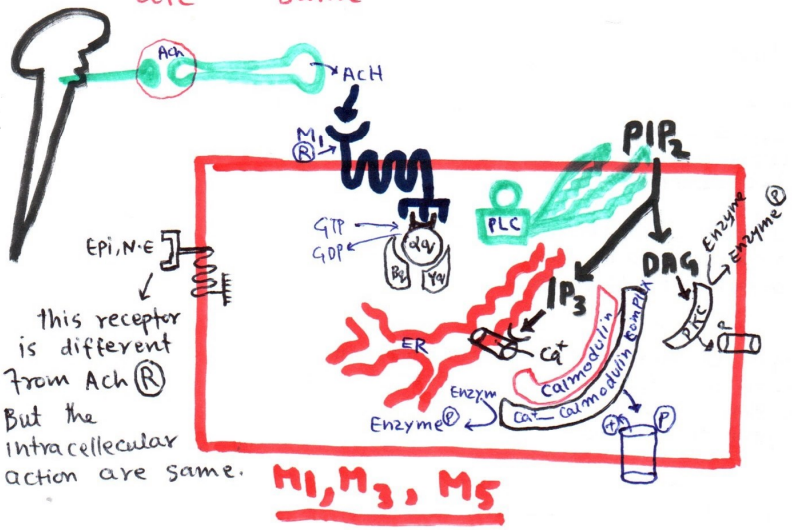
All Muscarinic receptors are G Protein coupled Some are excitatory & some are inhibitory



M_1, M_3, M_5 — Excitatory

M_2, M_4 — Inhibitory

① Mechanism of action of M_1, M_3 & M_5 are same



* Epineprine & N·Epinephrine also bind with Gq protein
* Angiotensin II is also coupled with Gq proteins

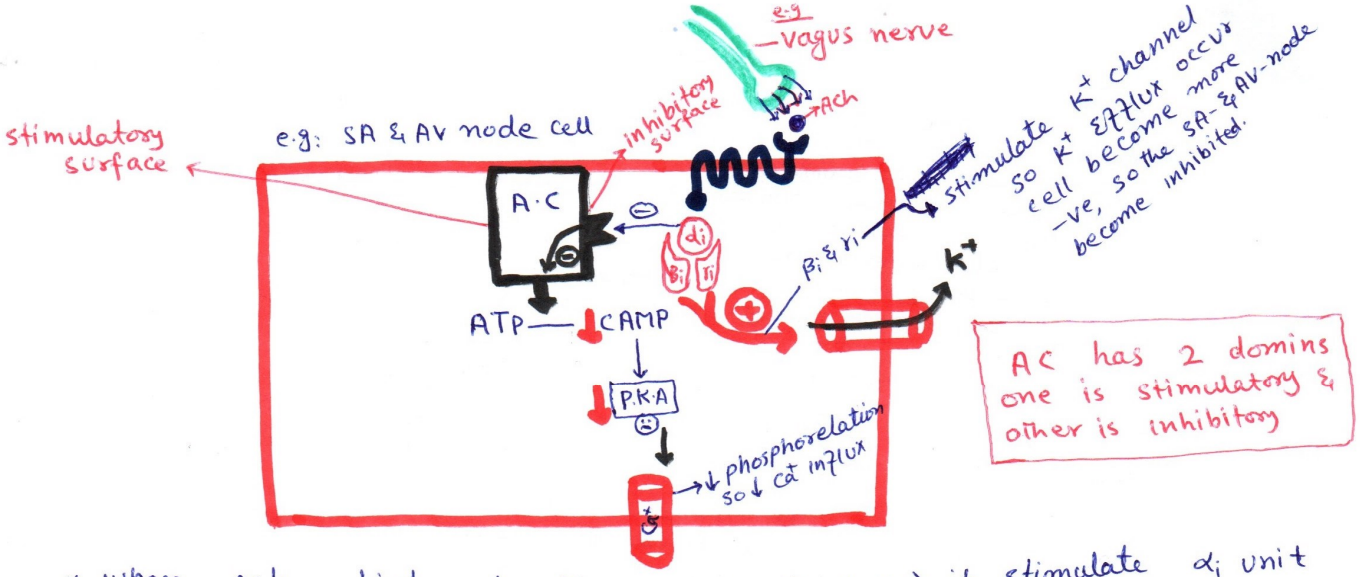
GIT also has M_3 receptors

when the Ach bind with G coupled protein receptor (M_1, M_3, M_5), the α_q unit are phosphorelated, & become highly energized, & stimulate the phospholipase-c (PLC), The PLC breakdown PIP_2 (Present on membrane) into IP_3 & DAG.

* The IP_3 stimulate Ca^+ channel of Endoplasmic Reticulum & alot of Ca^+ release from ER: the Ca^+ bind with Calmoduline & Ca^+–Calmoduline complex are formed. the complex a phosphorelate some enzymes & also phosphorelate channels present on membrane so alot of cations come in.
* The DAG activate Proteine kinase-c (PKC), which phosphorelate some enzymes & also open channels present on membrane so alot of cations come &: so as cell start its activity

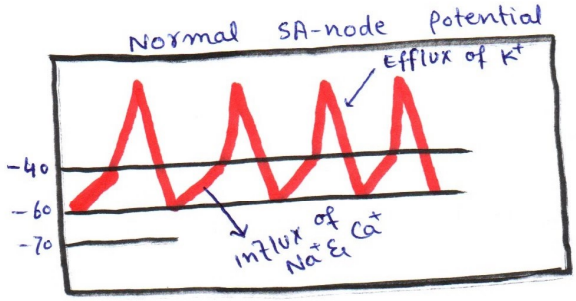
② Mechanism of action of M_2 & M_4 are same.

vagus cause bradycardia (inhibition)

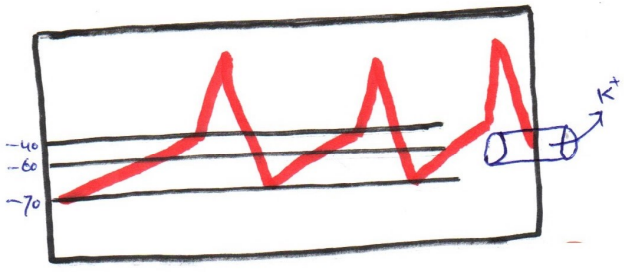


* when Ach bind to its receptor (M_2 & M_4) it stimulate α_i unit which inhibit Adenyl cyclase, so conversion of ATP into cAMP decrease; so decrease protein kinase-A, as result Ca^+-channel phosphorelation decreases, Ca^+ influx to cell become decrease → ↓ cell activity.
* the β_i & r_i units opens K^+-channels, alot of K^+-efflux occur, cell become more negative, & thus inhibitied.

Due to no catin influx, & ↑ efflux of catine cell become more electronegative, & inhibited.

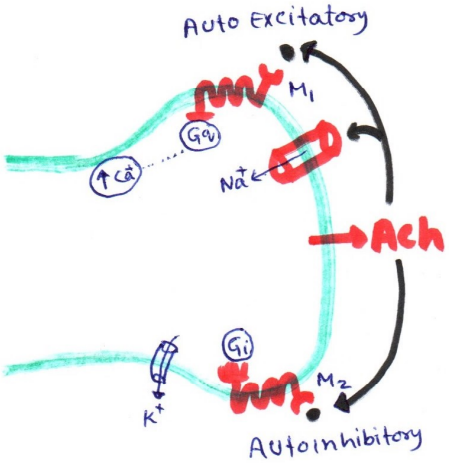


Action potential produced by normal SA-node.



If M_2 receptor come into action, cell become more hyperpolarized b/c:
① No catines (Na^+, Ca^+) come in &
② ↑ K^+ efflux,
So on this way the Action potential will take more time, so ↓ SA-node action; on this way bradycardia occur.

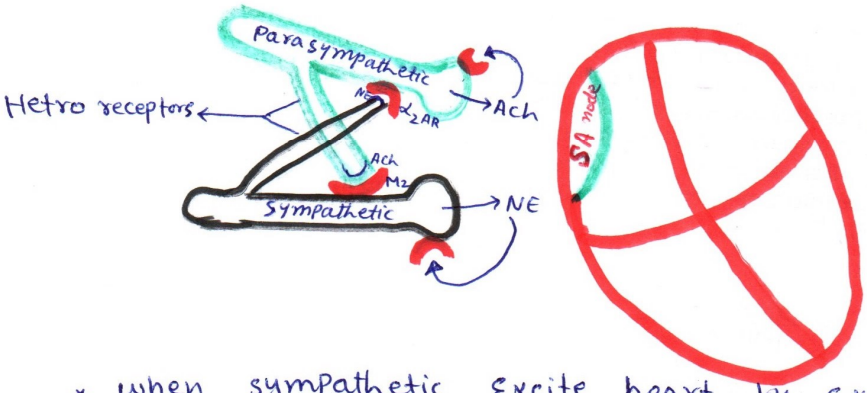
Autoregulation of Acetylcholin



* If the presynaptic membrane have M_2 receptor, when it is stimulated by Ach, so the cell become inhibited

* The Excitatory receptor on presynaptic membrane may be:
  * Nicotinic receptor OR
  * M_1 Receptor

  when these are stimulated by Ach, Catines in cell ↑, cell are stimulated.



* Sympathetic ↑ SA node activity
* Parasympathetic ↓ SA node activity

* when sympathetic Excite heart by Excitation of same time it Cause inhibition of Parasympathetic Nervous system.

* when parasympathetic inhibit heart, it also inhibit adrenergic system.

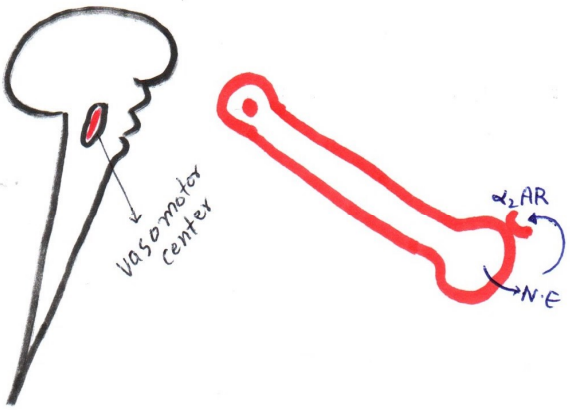
Both Sympathetic & Parasympathetic have auto receptors also stimulated by the same neurotransmitter.

e.g PSNS ⇒ Ach
SNS ⇒ E-pinephrine

Adrenergic receptor on PSNS is called Hetroreceptor.
cholinergic receptor on SNS is called Hetro receptor also.

* Post junctional membrane are influenced by Neurotransmitter.
* Pre junctional membrane are also influenced by " " by having Autoreceptor & Hetro receptors.

Clonidine ⇒ Stimulate α_2AR, Coupled with α_i So cell become inhibited.



* Drugs which stimulate α_2 will inhibit further release of Neurotransmitters

* Drugs which inhibit α_2 will increase further release of neurotransmitters.

Tissue distribution of Cholinergic receptors

- **Nicotinic**
  - **Nn**: Present in CNS ganglion (both symp + Parasym)
  - **Nm**: Present in neuro muscular junction
- **Muscarinic**
  - M_1, M_2, M_3, M_4, M_5
  - CNS have all of Muscarinic (R)

PSNS concerned with Rest, digest & elemination

M_1 ⟶ CNS, ganglion
M_2 ⟶ CNS, heart tissues
M_3 ⟶ CNS, smooth muscles, glands, Endothelial cells
M_4 ⟶, M_5 ⟶ only present in CNS

Those tissues on which Parasympathetic post ganglionic fibers ends: & release Ach those tissue have Muscarinic receptor.
Muscarinic receptor are present on:

① CNS ② effector tissue ③ Muscarinic receptor are also present on tissues where postganglionic cholinergic sympathetic fibers ends (ie: sweat gland)

④ There are some tissue where there is no direct cholinergic supply but they have Muscarinic receptor:
e.g = Endothelium of Blood vessele has M_3

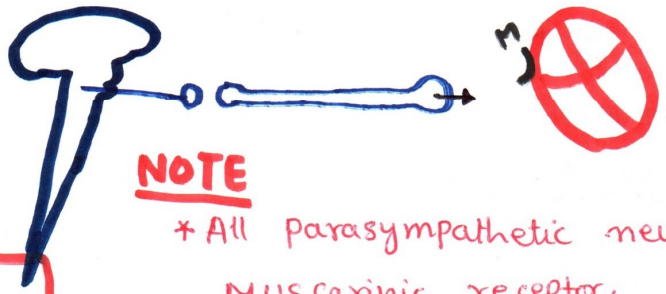
In blood vessele there is no significant Acetylcholine act b/c Ach are destroyed by choline esterase rapidly.

Cholinesterase

Butylcholinesterase
* Present in plasma
* also called Pseudocholinesterase
* These are also called non-specific chdinesterase

Acetylcholin esterase
* present in tissues
* also called True cholinesterase
* These are also called specific choline esterase

Drugs which are cholinergic agonist (Muscarinic R) are also called parasympathomemitic drugs



* Parasympathetic activated during rest
* sympathetic activated during stress

NOTE
* All Parasympathetic neuroeffector sites have MUScarinic receptor.
* sympathetic work diffusly
* Parasympathetic work localized & descrete.
  - If this was diffuse at the same time lacrimation, salivation, sweating, urination, defecation ...etc occurs.

Rest diges & Elimination

Function of Para sympathetic

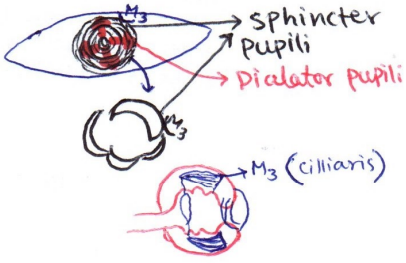
How Parasympathetic work

① EYE

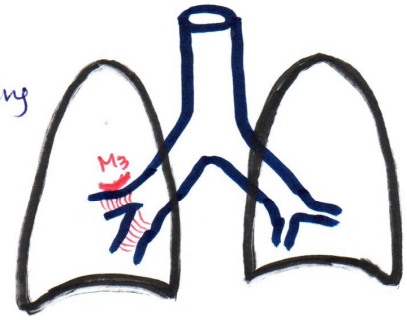
ⓐ Pupil Constriction = sphincter pupili has M_3 receptor, so when stimulated, It will constricted

ⓑ cilliaris contract = cilliaris are contracted & make the lens globular So person accomudate for near vision

ⓒ ↑ lacrimation = M_3 → lacrimal gland



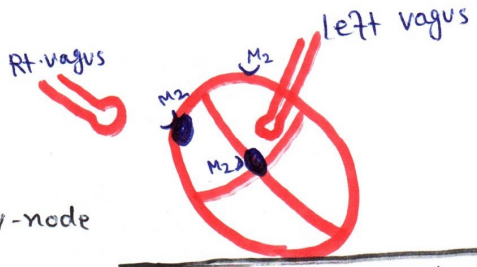
(2) Respiratory system



ⓐ Slightly broncho constriction → b/c during rest less O_2 are needed.

ⓑ ↑ Mucocilliary mechanism
ie ↑ bronchial glands secretions
So cholinergic drugs should not be given in Asthma patients.

(3) Cardiac



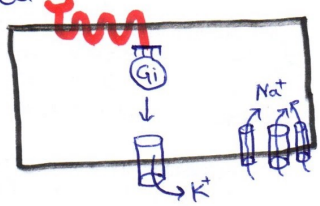
ⓐⓒ ↓ HR (Bradycardia) due to inhibition of SA-node

ⓑ AV-block ⇒ due to inhibition of AV-node

ⓒ decrease contractility
- ⊖ Chromotropic (by inhibition of SA-node)
- ⊖ Dromotropic (by inhibition of AV-node)
- ⊖ Inotropic (by inhibition of atria)

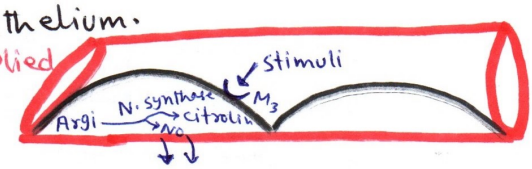
SA, AV-node & Atria has M_2 receptors.
* ventricular Myocardium is not significantly supplied by parasympathetic nervous system.

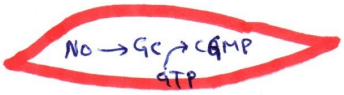
when M_2 receptor on atria are stimulated Action potential of atria is increased, while refractive period of atria is decreased B/c M_2 activation can lead to loss of K^+ & Cell become electronegative, when cell become too much electronegative, there is automatic opening voltage gatted Na^+ channels & it stimulate the cell



(4) vascular system

There is no significant amount of Acetylcholine in the blood b/c it is destroyed. But even if Neurotransmitter is released or enter into blood as a drug it acts on M_3 receptor of endothelium.
Most of vascular system is not supplied by cholinergic Ⓡ system
when stimuli come to M_3 receptor of vessele Endothelium, activate the Endothelium, in which Nitric oxide synthase enzyme are activated



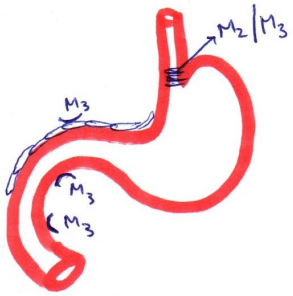


The nitricoxide synthase (N.S) convert Arginine to citroline & Release NO, the NO diffuse in media & stimulate Guanyl cyclase. which convert GTP into cGMP, the cGMP cause relaxation of smooth muscle & BP goes down.
Previously NO were called Endothelial smooth muscle relaxant.

Arginin —Nitricoxide synthase→ citrolin] within Endotheliam

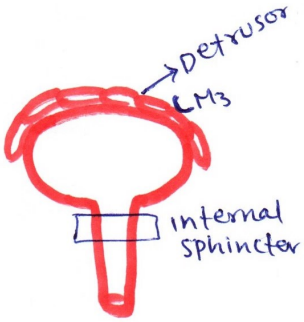
NO → G.Cyclase (GTP) → cGMP → Smooth muscle Relax] in Media

(5) GIT



ⓐ Salivary gland has M_3 (↑ secretion)
ⓑ Gastric secretion (M_3) (↑ secretions)
ⓒ duodenum, jejunum, Illium, Pancrease, billiary system has M_3 (↑ secretions)
ⓓ ↑ peristalsis
ⓓ ↑ed Tone
ⓕ Sphincters has M_2 & M_3 while M_3 dominant
ⓖ large intestine (M_3) ⇒ defecation

(6) urogenital system



ⓐ detrusor Contraction ⇒ Bladder contraction
ⓑ Internal sphencter is under powerful Controle of sympathetic Nervous system but when M_3 receptor of detrusor are stimulated by Acetylcholin, it will also inhibit sympathetic receptor, so sphincter relax & urination occur

All Parasympathetic Nervous system activity are not stimulated it once.
ⓒ Penile erection ⇒ Ach → M_3 → NO → Relax smooth muscle
ⓓ ↑ed Veginal secretion / Lubrication

(7) sweat gland has M_3 receptor

what happend to body when there is cholinergic overflo

close the pupil, Inhibit the heart & Secrete & eleminate

End of cholinergic system

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