"Relax. He could just be looking for fun."

PARASYMPATHOMIMETICS

By Dr. Ayesha Jamil

Describe the

Synthesis

Storage

Release

Binding

degradation

Recycling of Choline & Acetate

Describe in detail the mechanism of action of different types of receptors

Describe the concept of autoreceptors and hetroreceptors with their clinical significance

Describe the pharmacological response of parasympathetic stimulation of cholinergic receptors

Classify cholinomimetics

Describethe pharmacotherpay of glaucoma

Describe in detail the mechanism of action pilocarpine in glaucoma

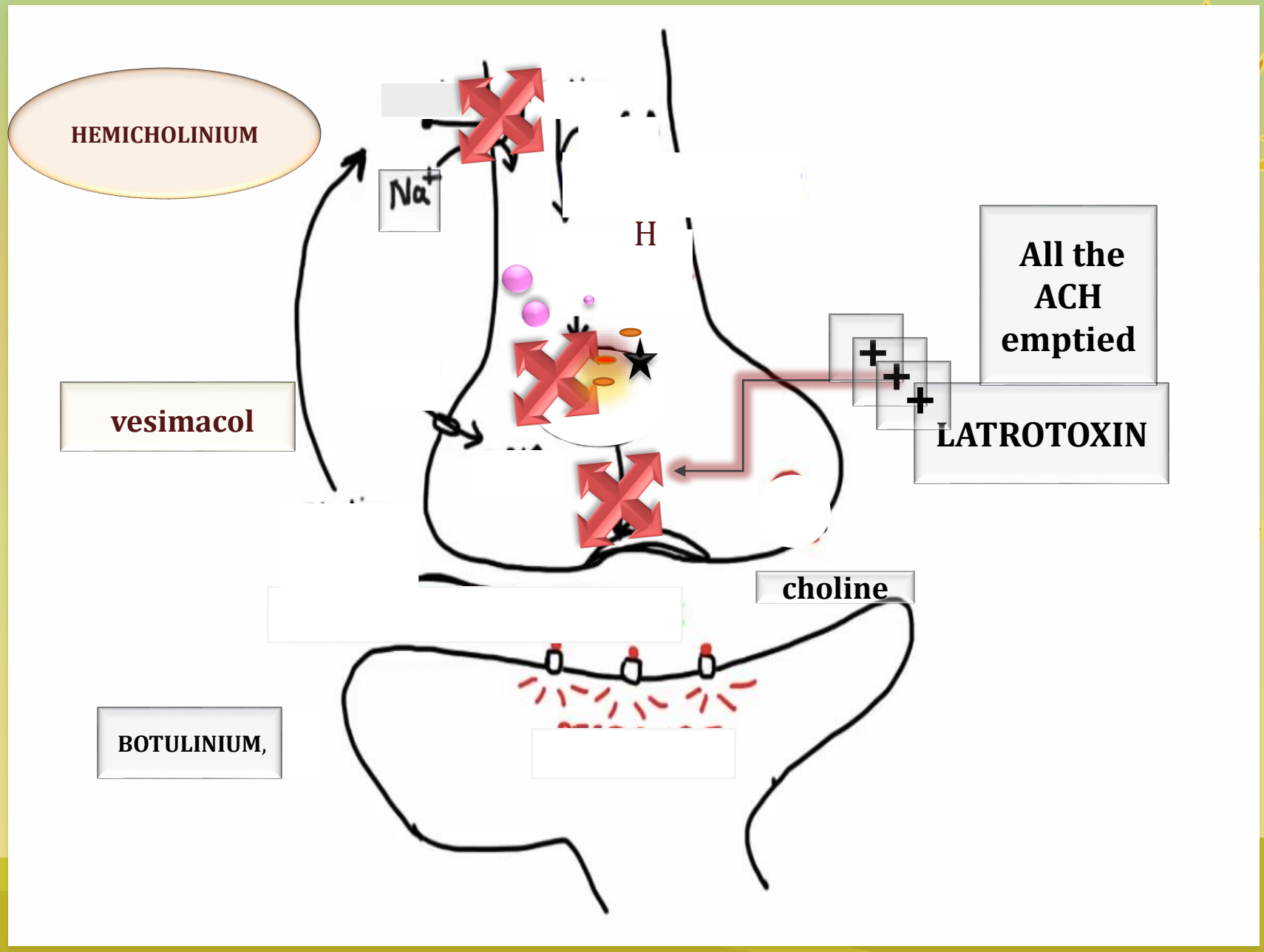
Describe the therapeutic uses of direct and indirect cholinomimetcs

Synthesis Of Acetylcholine

Storage Of Acetylcholine

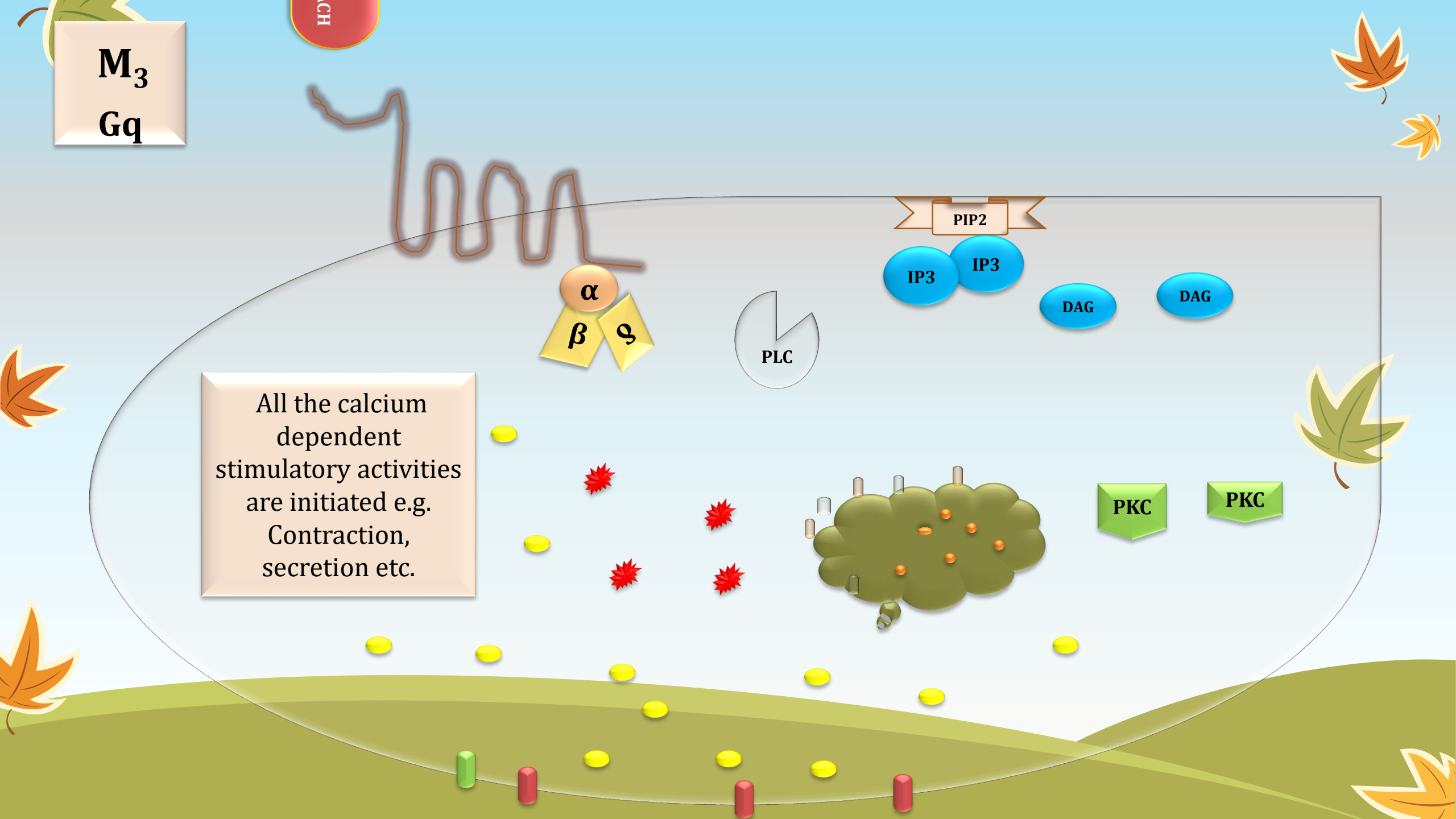
Release Of Acetylcholine

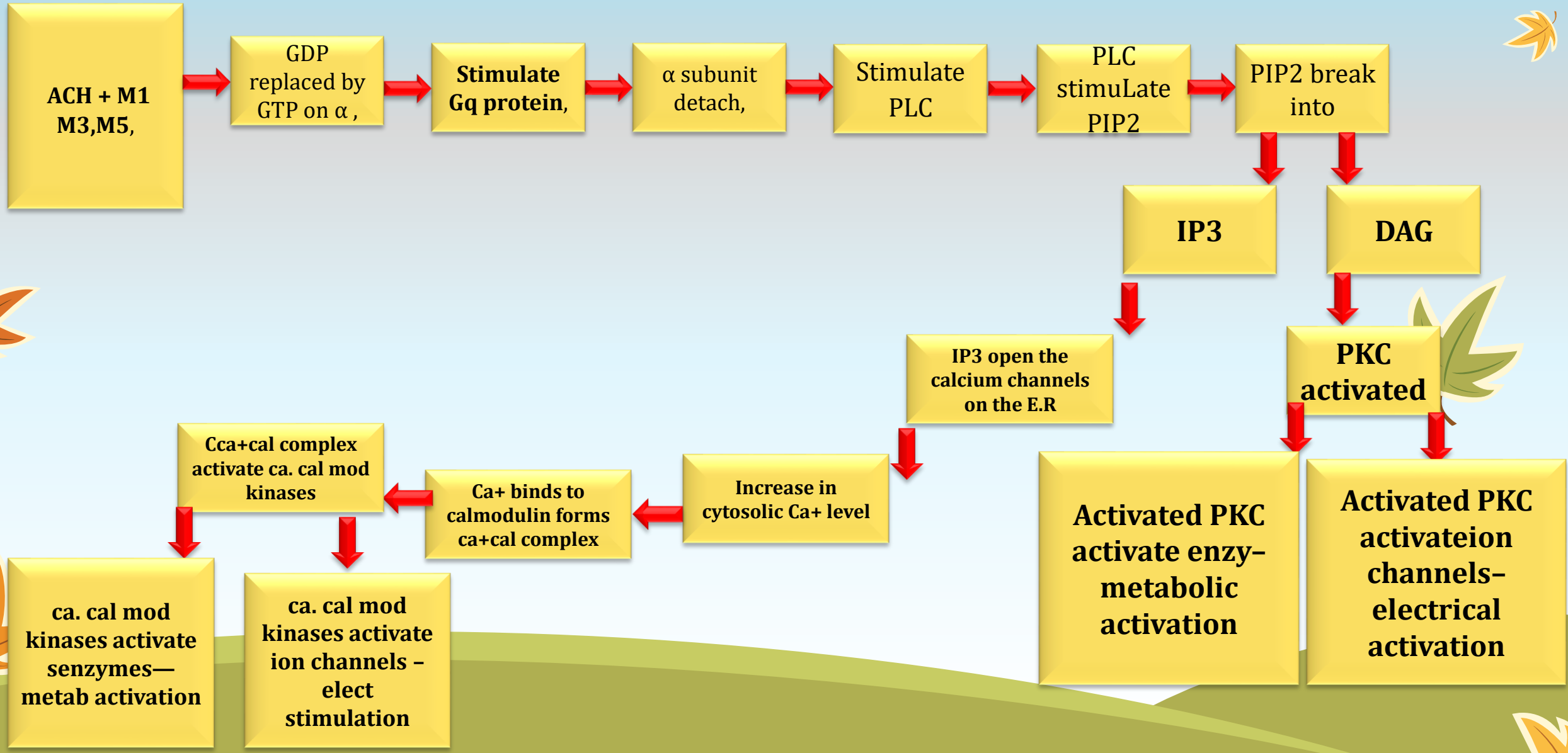
Degradation Of Acetylcholine



CHOLINORECEPTORS

M1, M2, M3,M4,M5.


M_3
Gq
ACH
α
β
ϒ
PLC
PIP2
IP3
IP3
DAG
DAG
PKC
PKC
All the calcium dependent stimulatory activities are initiated e.g. Contraction, secretion etc.


ACH + M1 M3,M5,
GDP replaced by GTP on α ,
Stimulate Gq protein,
α subunit detach,
Stimulate PLC
PLC stimuLate PIP2
PIP2 break into
IP3
DAG
IP3 open the calcium channels on the E.R
PKC activated
Increase in cytosolic Ca+ level
Ca+ binds to calmodulin forms ca+cal complex
Cca+cal complex activate ca. cal mod kinases
ca. cal mod kinases activate senzymes— metab activation
ca. cal mod kinases activate ion channels – elect stimulation
Activated PKC activate enzy– metabolic activation
Activated PKC activateion channels– electrical activation

Gq coupled receptors

α_1

M3

M1

M5

Angiotensin 2 receptors

Gq coupled receptors located in

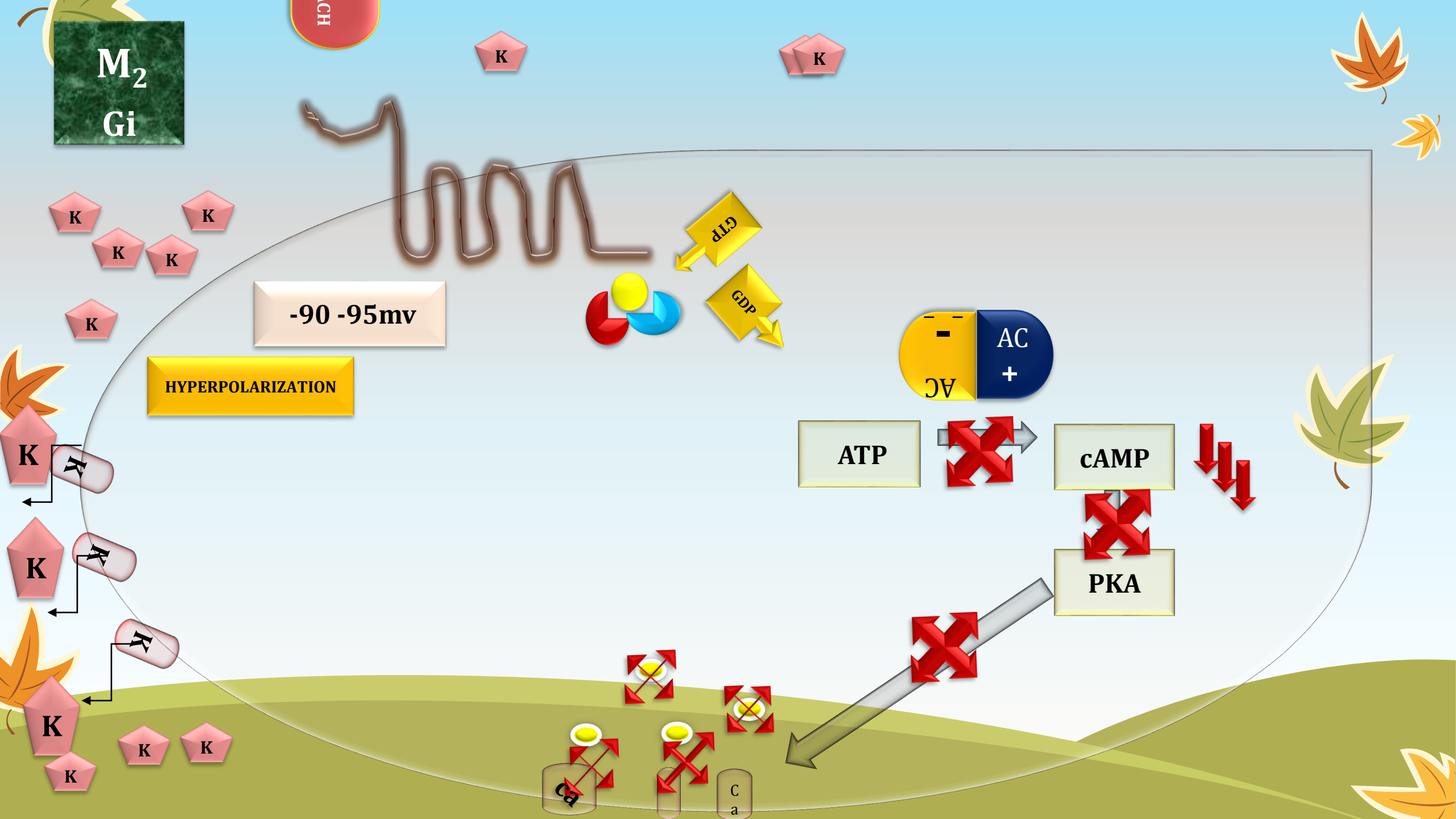
Smooth muscle----- contraction

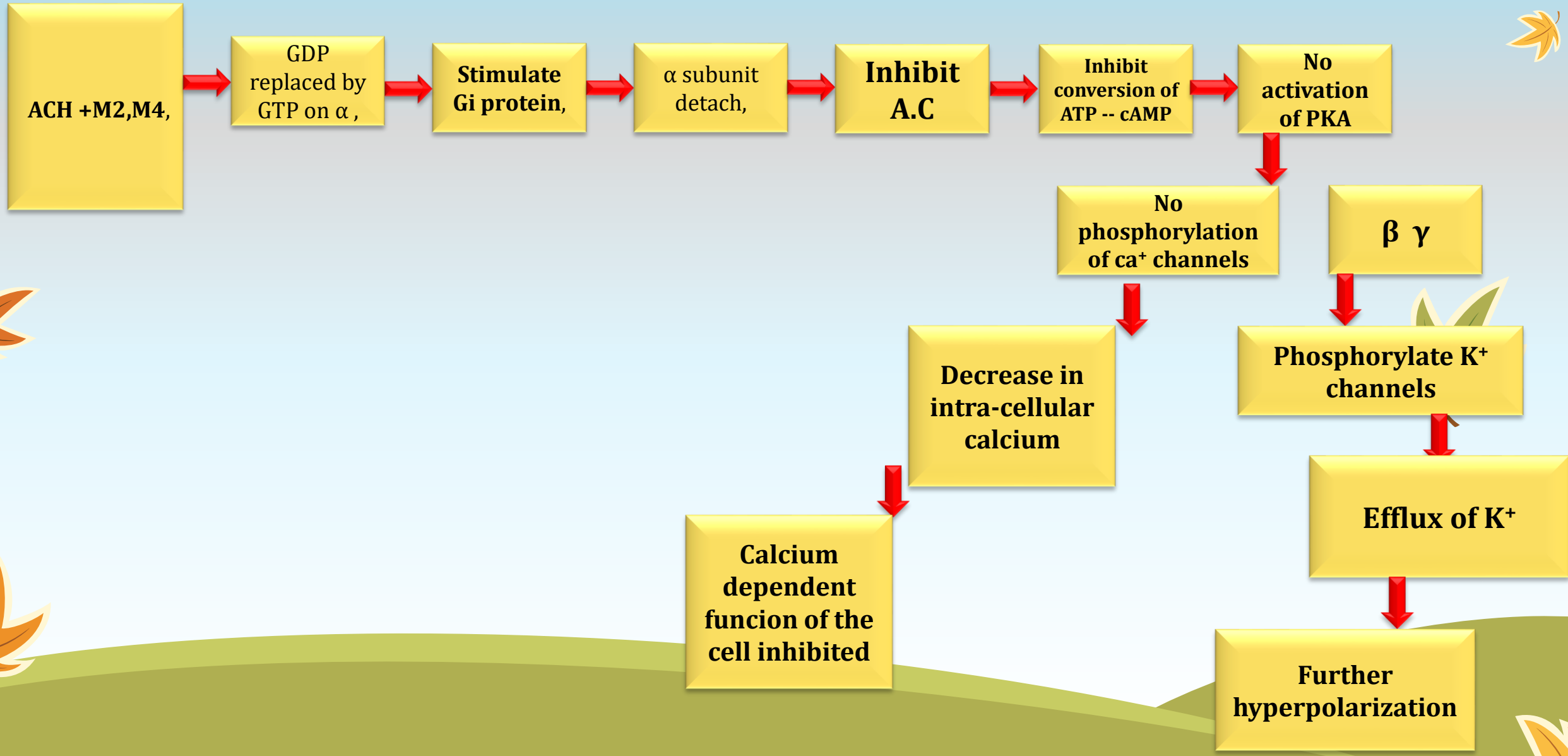
e.g, EYE---sphincter pupilea---

contract-----meiosis--- M3.

GIT----contraction --- increased peristalsis--- M3

Glandular ----------secretion


M2
Gi
ACH
K
-90 -95mv
HYPERPOLARIZATION
GTP
GDP
AC
ATP
cAMP
PKA
Ca
Ca

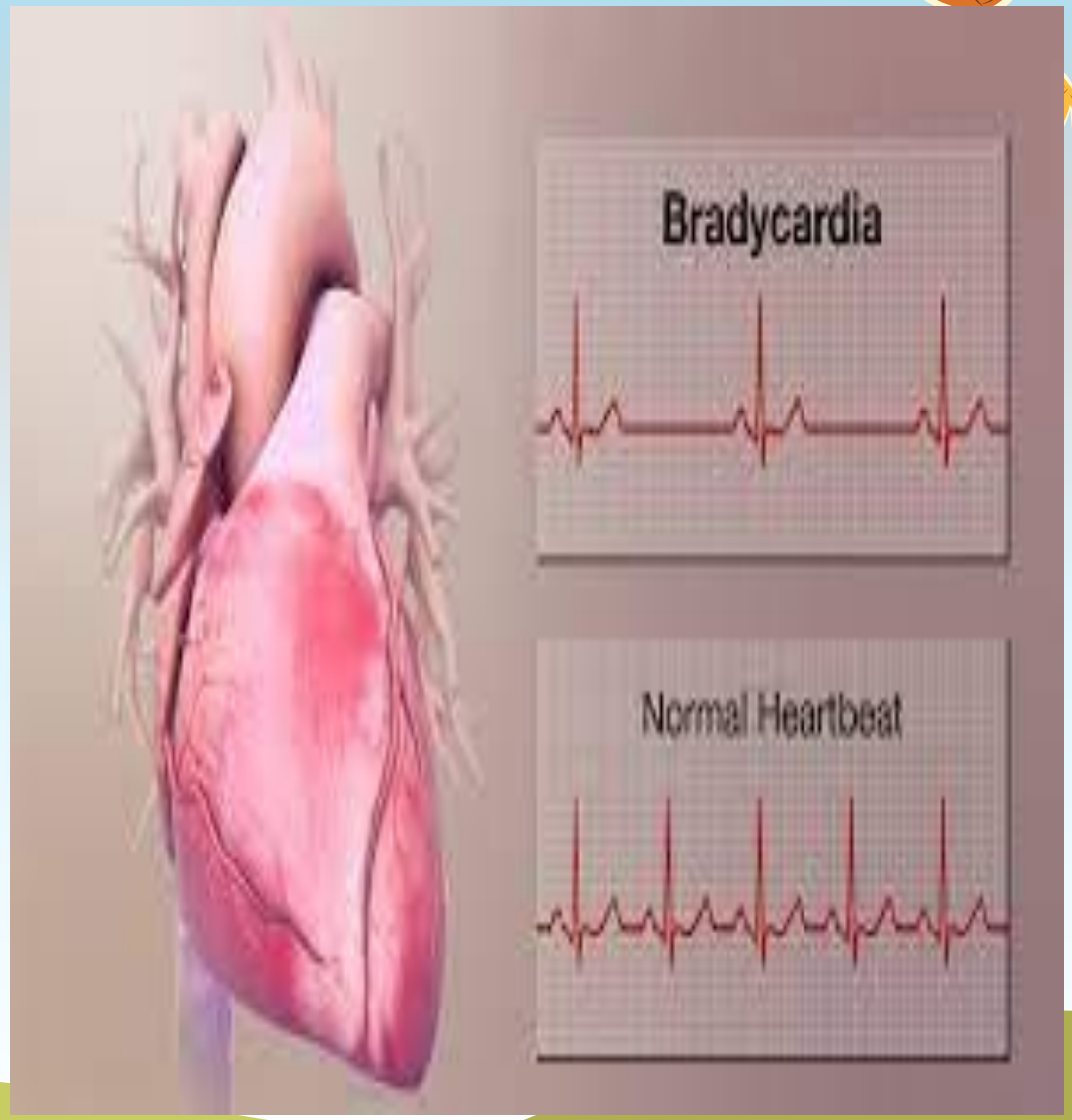

ACH +M2,M4,
GDP replaced by GTP on α ,
Stimulate Gi protein,
α subunit detach,
Inhibit A.C
Inhibit conversion of ATP -- cAMP
No activation of PKA
No phosphorylation of ca+ channels
β γ
Decrease in intra-cellular calcium
Phosphorylate K+ channels
Calcium dependent funcion of the cell inhibited
Efflux of K+
Further hyperpolarization

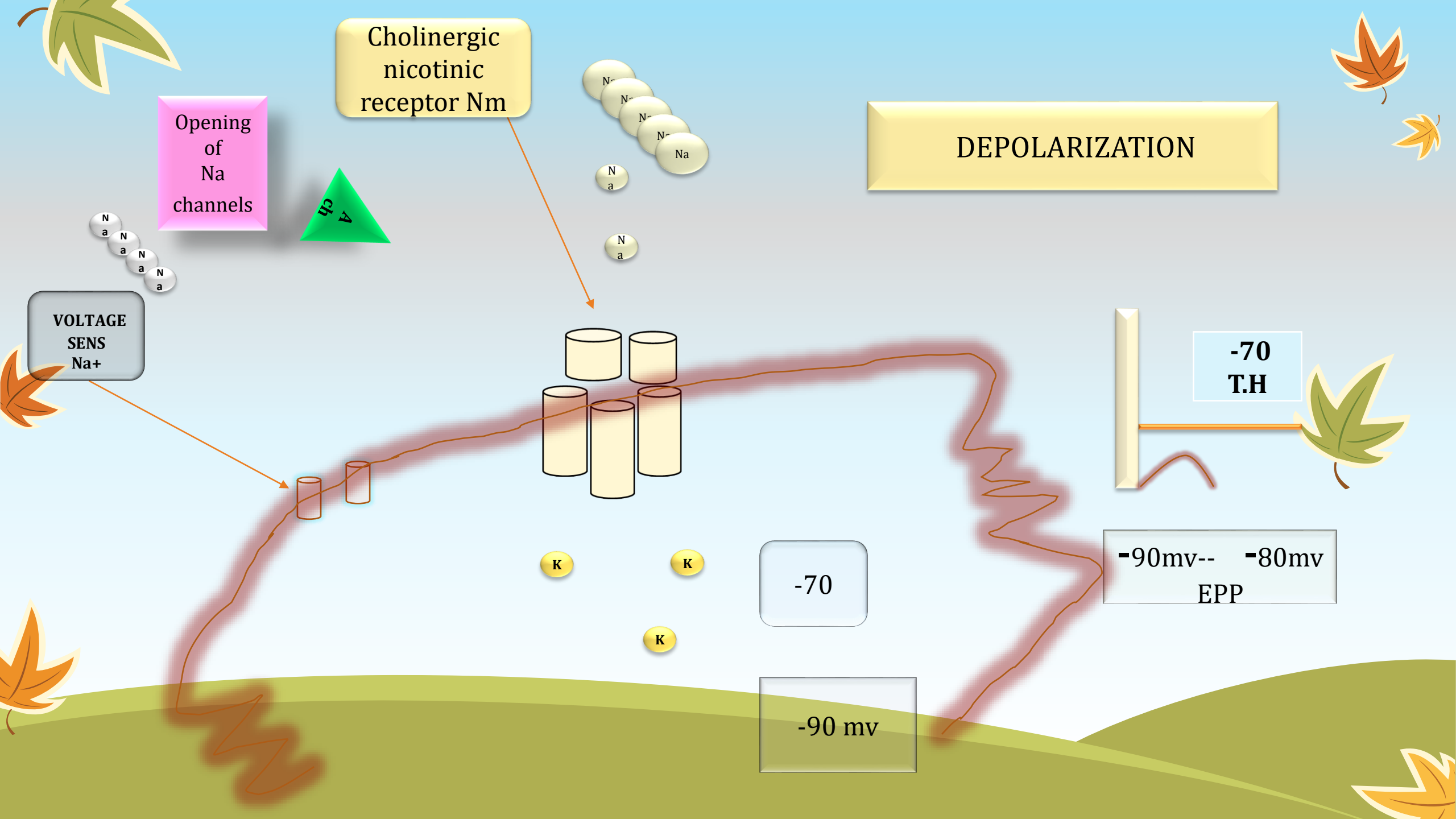
M2 RECEPTORS IN S.A NODE

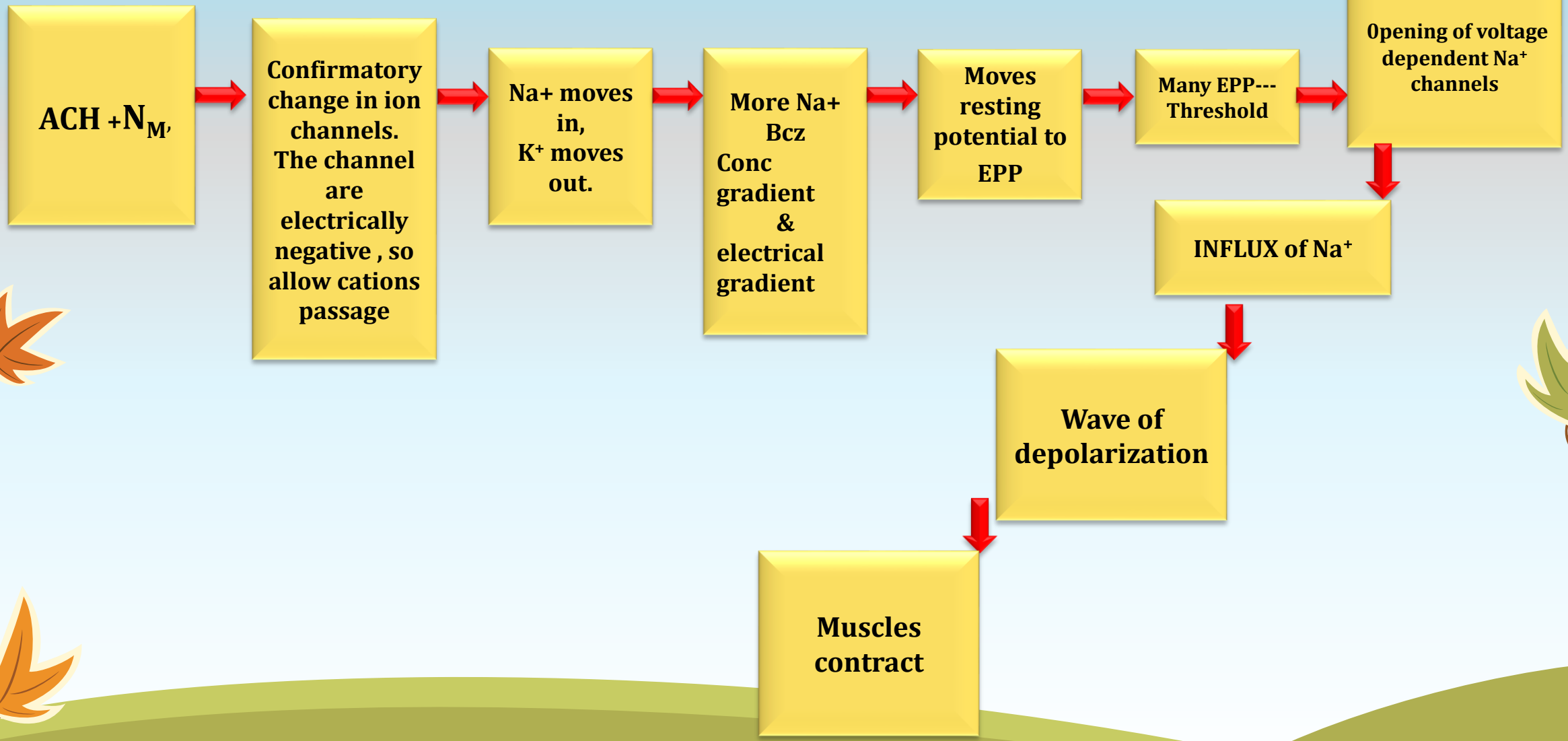
a. K^+ efflux---makes resting memb potential more negative. So greater time required to reach threshold potential.

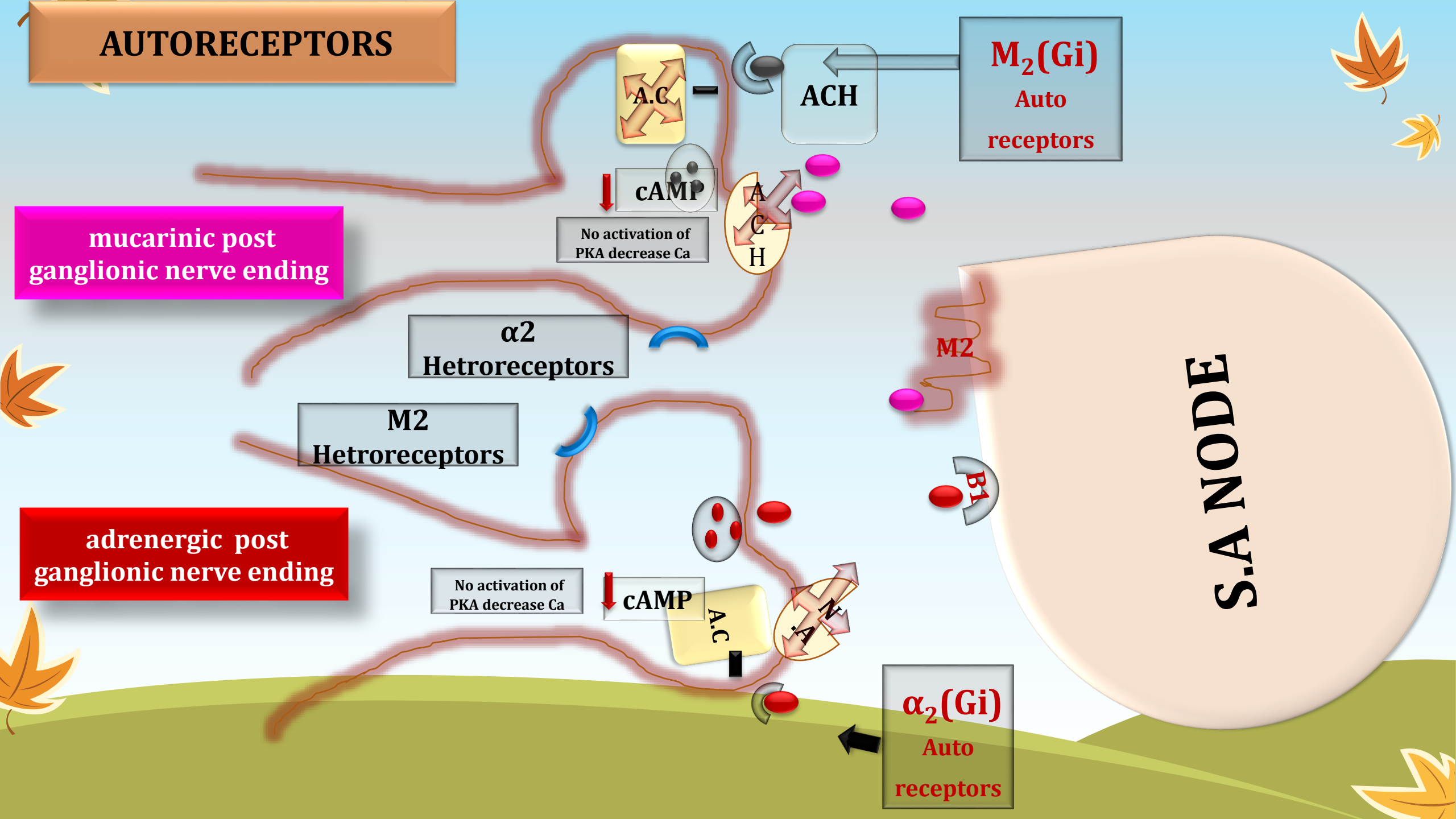
b. Inhibition of the opening voltage dependent Ca^+ channels also require greater time to induce depolarization.

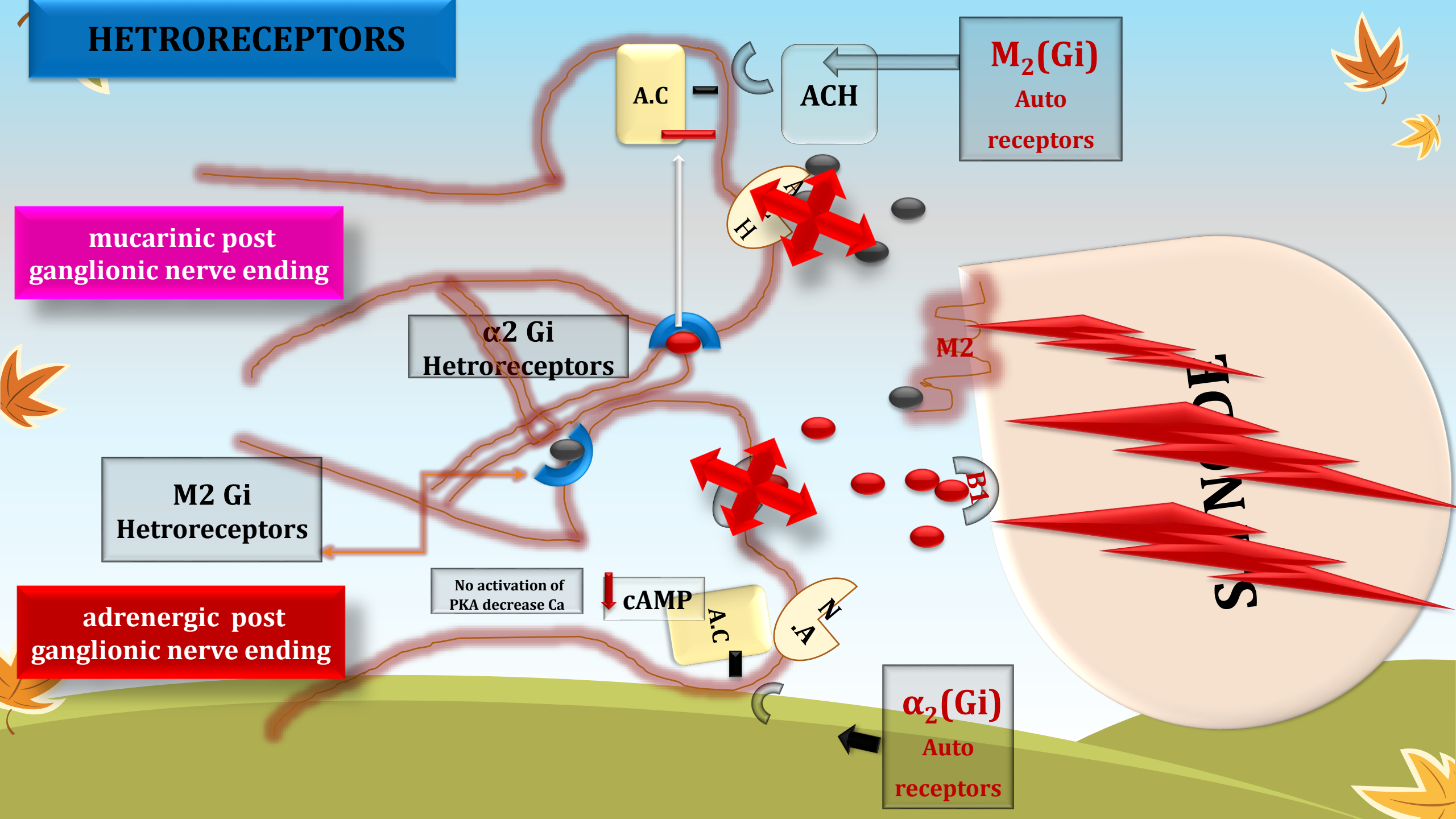
c. Bradycardia is produced.




Cholinergic nicotinic receptor Nm
Opening of Na channels
Ach
VOLTAGE SENS Na+
DEPOLARIZATION
-70 T.H
-90mv-- -80mv EPP
-70
-90 mv


ACH +$N_{M,}$
Confirmatory change in ion channels. The channel are electrically negative , so allow cations passage
Na+ moves in, K^+ moves out.
More Na+ Bcz Conc gradient & electrical gradient
Moves resting potential to EPP
Many EPP--- Threshold
0pening of voltage dependent Na^+ channels
INFLUX of Na^+
Wave of depolarization
Muscles contract

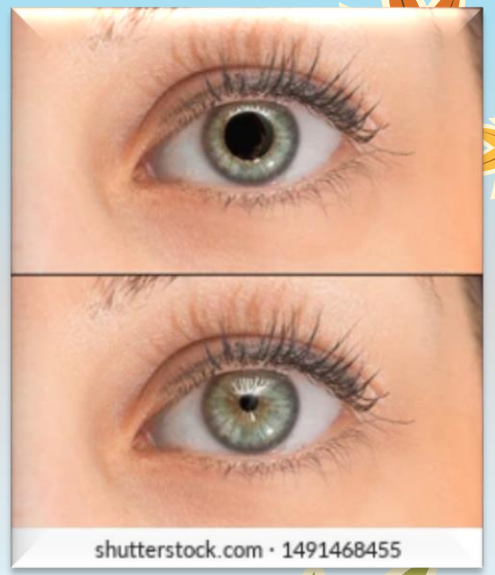

AUTORECEPTORS
mucarinic post ganglionic nerve ending
adrenergic post ganglionic nerve ending
A.C
ACH
M2(Gi)
Auto receptors
cAMP
No activation of PKA decrease Ca
A C H
α2 Hetroreceptors
M2 Hetroreceptors
M2
B1
S.A NODE
No activation of PKA decrease Ca
cAMP
A.C
N. A
α2(Gi)
Auto receptors


HETRORECEPTORS
mucarinic post ganglionic nerve ending
adrenergic post ganglionic nerve ending
A.C
ACH
M2(Gi) Auto receptors
α2 Gi Hetroreceptors
M2 Gi Hetroreceptors
M2
B1
No activation of PKA decrease Ca
cAMP
A.C
α2(Gi) Auto receptors

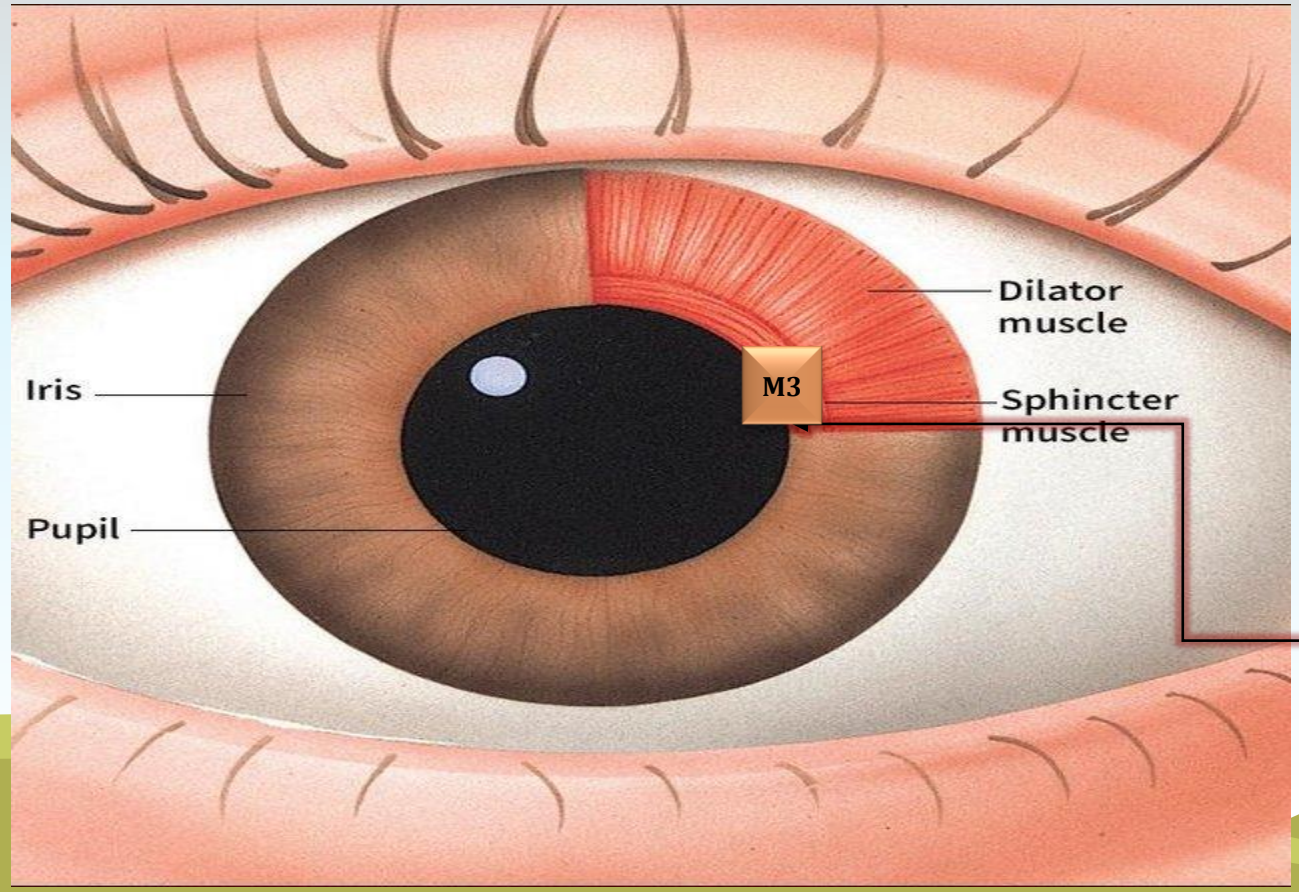
Distribution Cholino-Receptors And Their Pharmacological Effects

Rest & Digest & Eliminate

Parasympathetic stimulation effect of eye



Restricts the entry of light into the eye.



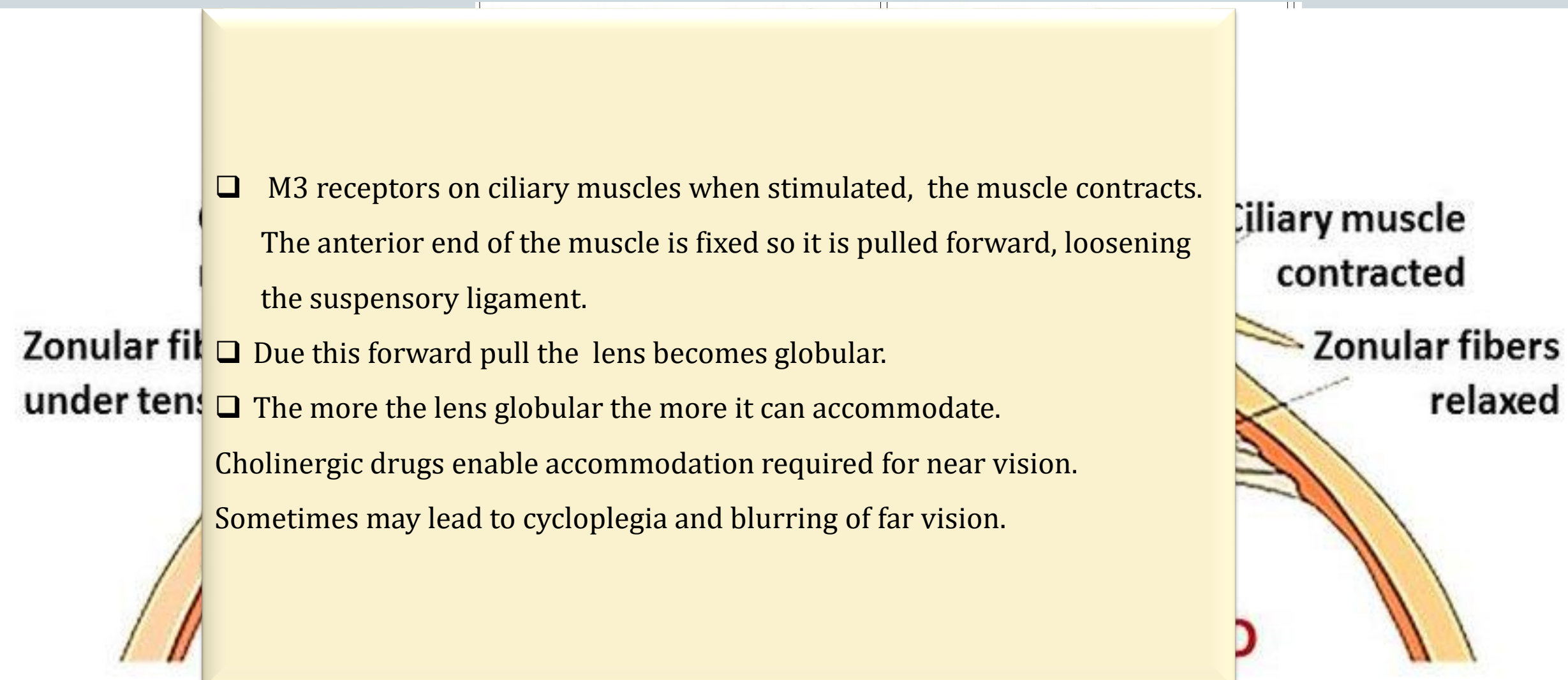
M3(Gq) receptors

Parasympathetic stimulation effect of eye

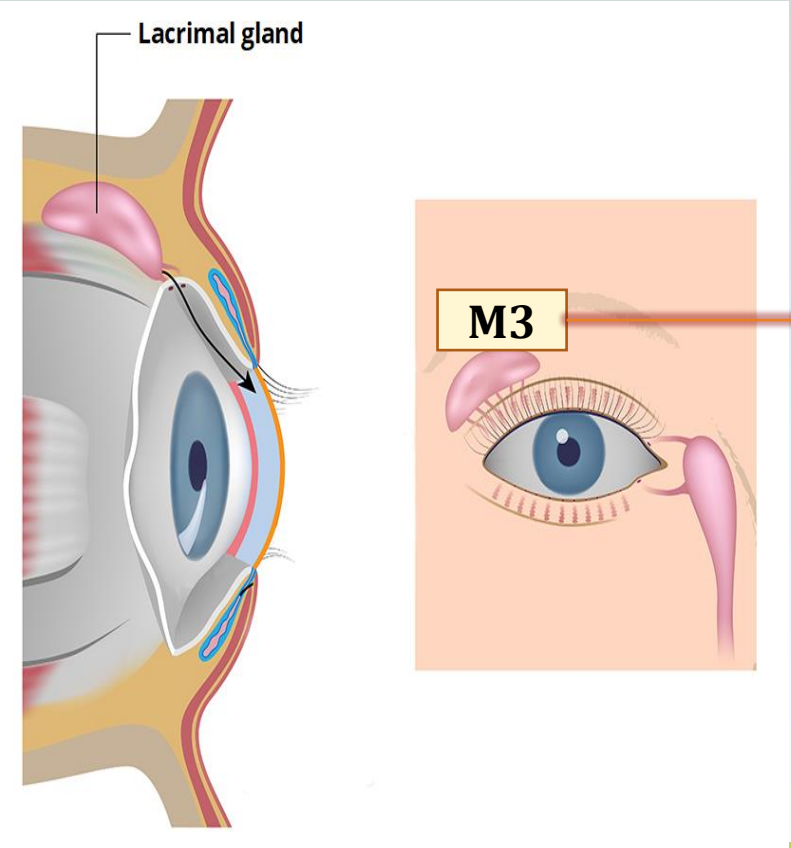
- M3 receptors on ciliary muscles when stimulated, the muscle contracts. The anterior end of the muscle is fixed so it is pulled forward, loosening the suspensory ligament.
- Due this forward pull the lens becomes globular.
- The more the lens globular the more it can accommodate.

Cholinergic drugs enable accommodation required for near vision.

Sometimes may lead to cycloplegia and blurring of far vision.

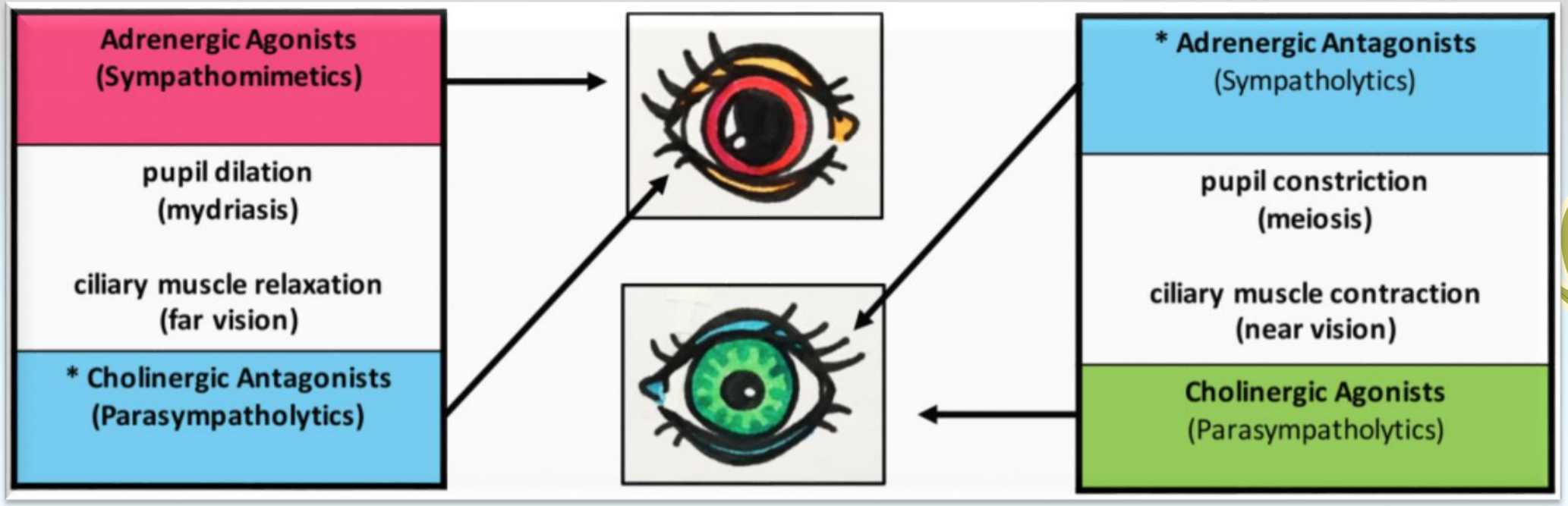


Parasympathetic stimulation effect of Eye

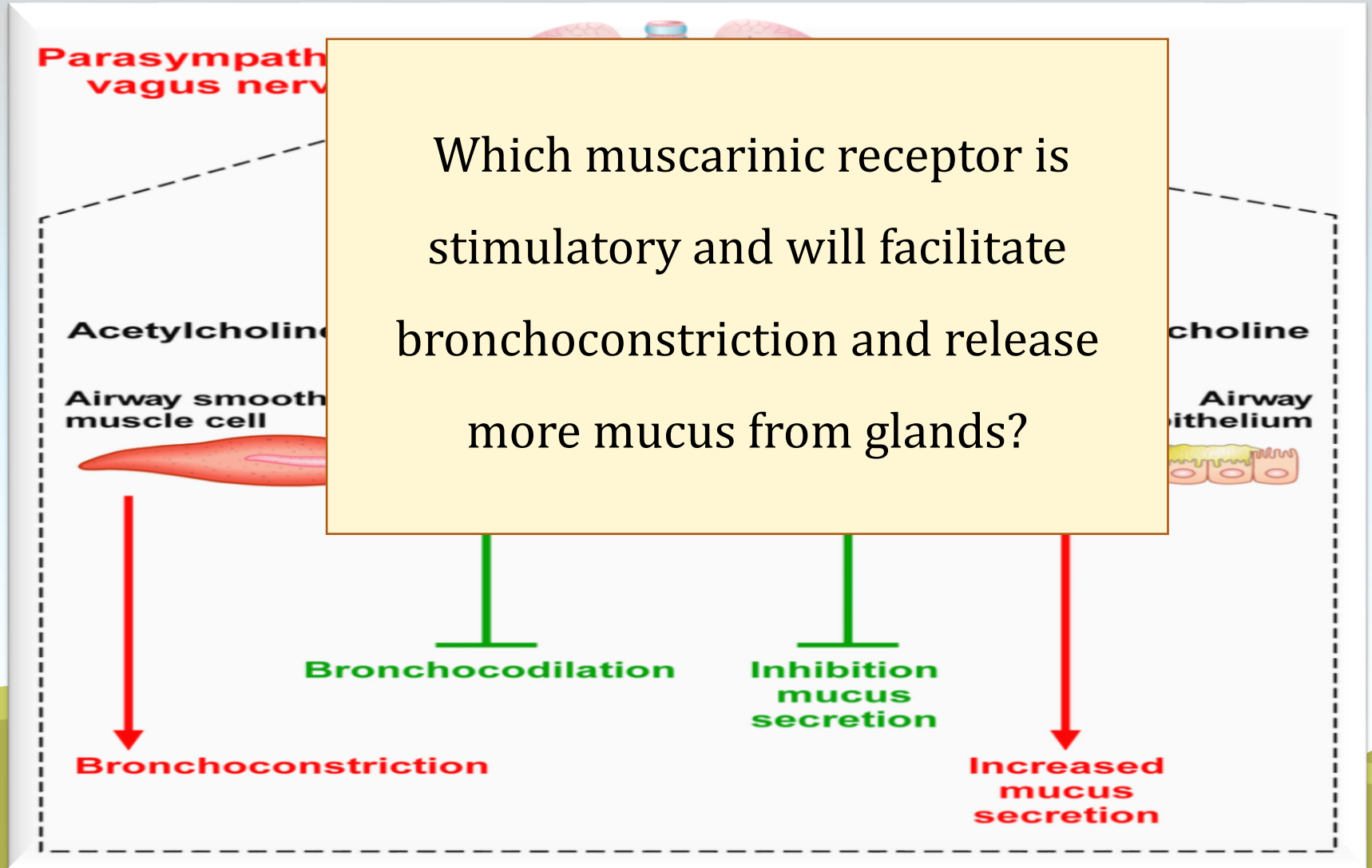


Simulation of M3 receptors on the lacrimal glands promote lacrimation

Gq


Adrenergic Agonists
(Sympathomimetics)
pupil dilation
(mydriasis)
ciliary muscle relaxation
(far vision)
* Cholinergic Antagonists
(Parasympatholytics)
* Adrenergic Antagonists
(Sympatholytics)
pupil constriction
(meiosis)
ciliary muscle contraction
(near vision)
Cholinergic Agonists
(Parasympatholytics)

Parasympathetic Stimulation Effect On Respiratory System

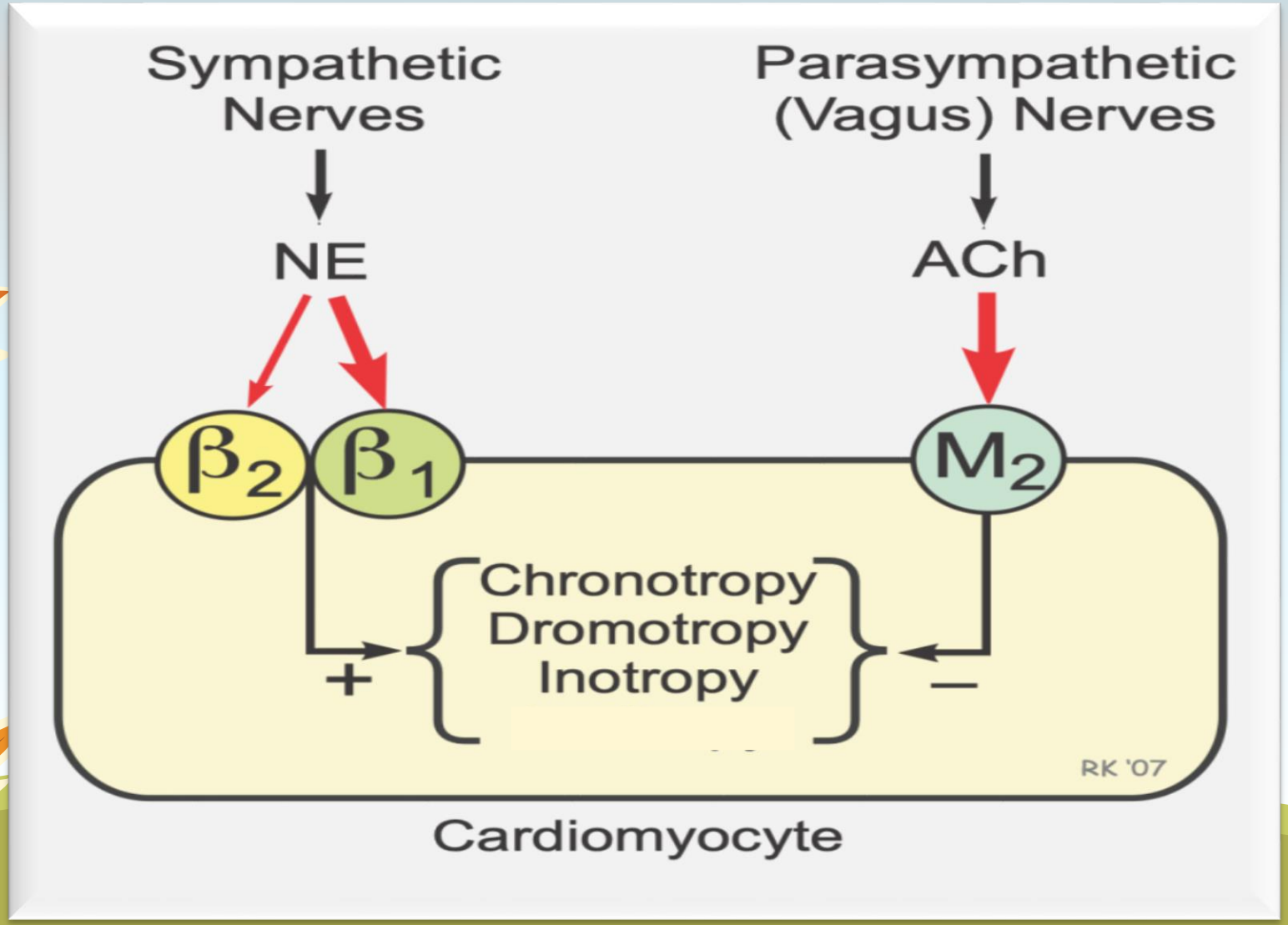


Which muscarinic receptor is stimulatory and will facilitate bronchoconstriction and release more mucus from glands?

While relaxing O_2 requirement is reduced. Mucocillary clearance active, so more secretions needed.

So a little bronchoconstriction at rest.
To facilitate mucocillary clearance a bit more mucus secretion .

Parasympathetic stimulation of heart



Parasympathetic (vagal) innervation mainly in the Atria.

Slows down the heart rate

Slows down the A.V conduction.

Reduces the force of contraction **(INIBITORY EFFECT)**

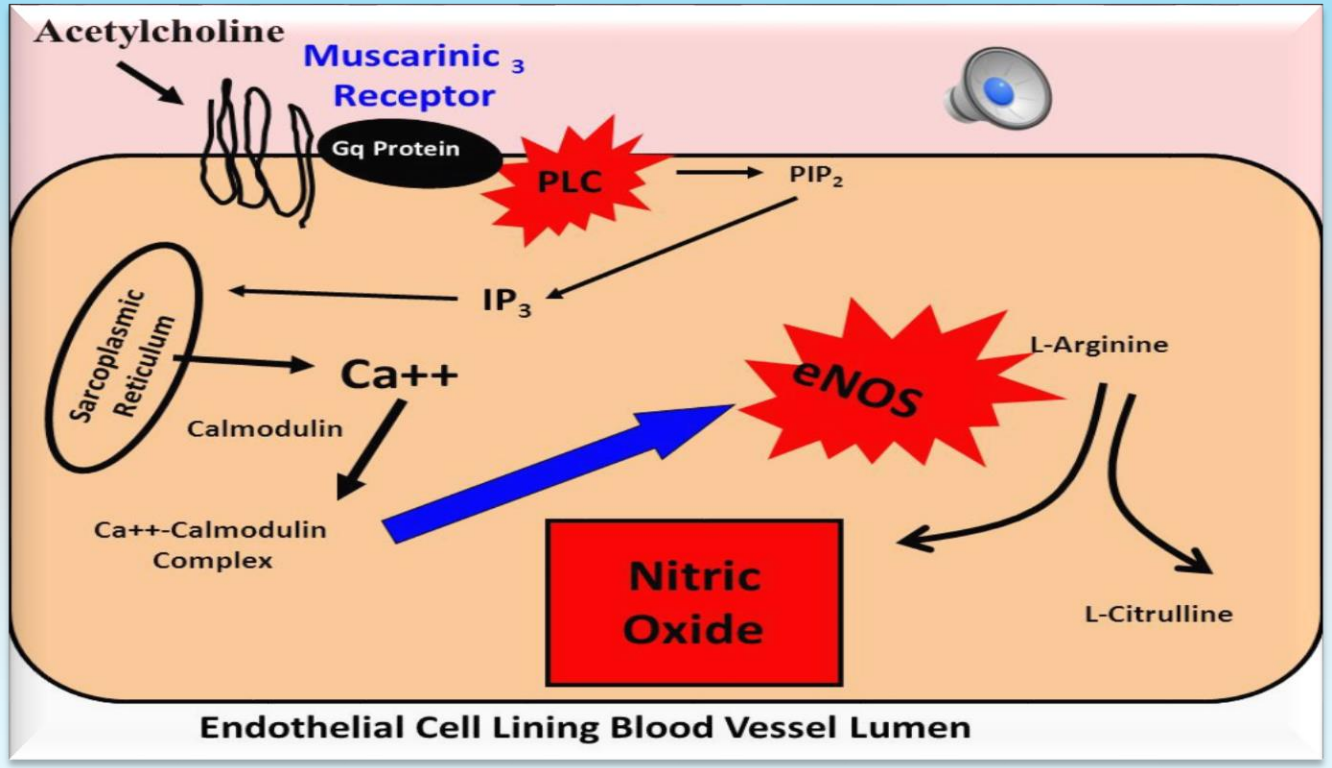
WHICH COULD BE THE RECEPTOR?

Parasympathatic stimulation of Blood Vessels

Parasympathetic fibers innervate blood vessels in certain organs such as salivary glands, gastrointestinal glands, and in genital erectile tissue.

Parasympathatic stimulation of Blood Vessels

Endothelail cells have M3 receptors.



Nitric Oxide moves to media underlying

NO activate Guanylyl cyclase

GTP---------- cGMP

NO previouslt also called **EDRF. Endothelial relaxing factors.**

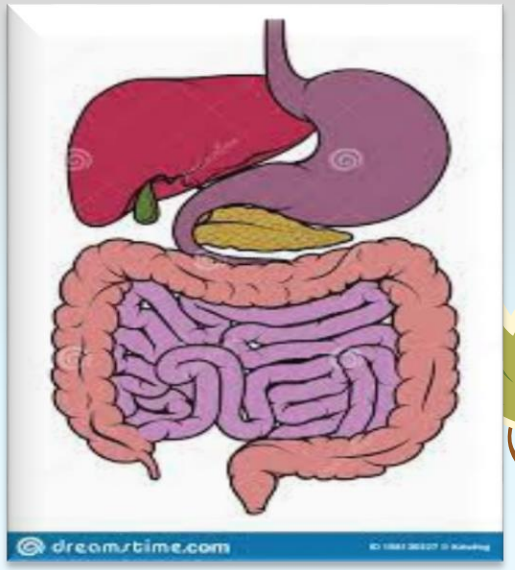
Parasympathatic stimulation ofGIT.

M3 receptors are present on the

Salivary glands-----increased secretions

Gastric glands ---- increased secretions

Also deudenal, jejeunal, colonic, biliary and pancreatic secretions are increased.



Defecation pathway is through parasympathetic innervation.

.

Internal anal sphinter relaxed through M2 receptors involuntary.

Ext anal sphincter relaxed voluntarily.

Parasympathatic stimulation of Urinary bladdar.

YOU VOID MOSTLY WHEN YOU ARE RELAXED

DETRUSOR muscle has M3 receptors.

There activation cause contraction of detrusor.

Internal urethral sphincter has adrenergic α1 receptor which maintain the tone of IUS.

Contraction of Detrusor (mechanical pressure) and inhibitory influence of ach on adrenergic presynaptic nerve endings (role of Hetroreceptors) relax the IUS and facilitate voiding.

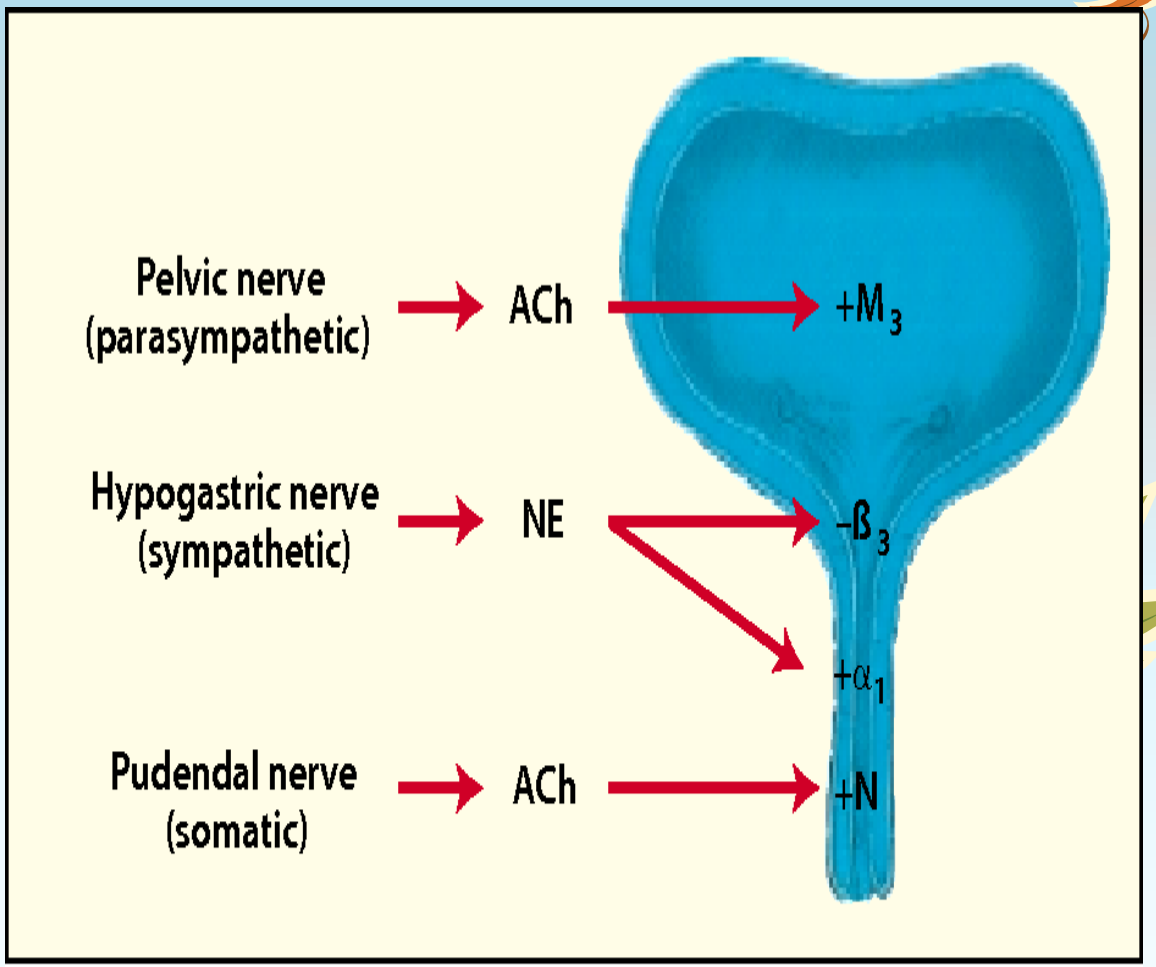


Figure 1. *Innervation of the lower urinary tract: The parasympathetic pelvic nerve stimulates the bladder detrusor muscle, mediated by muscarinic receptors (M_3) being activated by acetylcholine (ACh). The sympathetic hypogastric nerve stimulates urethral smooth muscle and inhibits bladder detrusor, mediated by α_1-adrenergic and β_3-adrenergic receptors, respectively. The somatic pudendal nerve stimulates striated muscle of the external urethral sphincter, mediated by ACh activating nicotinic (N) receptors. NE, norepinephrine. Plus and minus signs indicate neural stimulation and inhibition, respectively.*

Parasympathetic stimulation of genitalia

Parasympathetic stimulation causes stimulation of M3 receptors on the endothelial cell of t penile vasculature leading to erection in males.

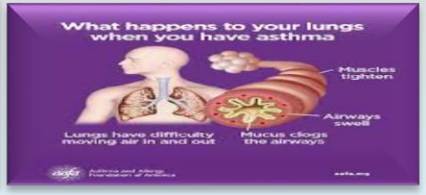
In female it causes increase in vaginal secretions.

CHOLINERGIC OVERFLOW

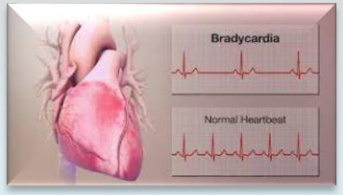
PUPIL CONSTRICT

Nasal secretion increase

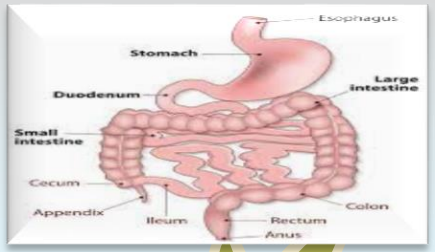
Increase salivation



Asthma like condition



Slowing down cardiac activity



Increased peristaltic movements

Lacrimation

Involutary voiding

Increased gastric secretions

May pass stools

CHOLINORECETORS

CNS	GANGLIA BOTH P.S & SYMP	NEURO-EFFECTOR SITES OF POST GANG P.S FIBERS	NEUROMUSCULAR JUNCTIONS

exclusive nicotinic drugs are actually CNS stimulants

cholinergic drugs

DIRECT ACTING

MUSCRINIC & NICOTINE

CHOLINE ESTERS

- ACH----------(M,N)
- METHACHOLINE---(M)

Choline is methylated

- CARBACHOL---------(M,N)
- **Acetate repalaced by carbamate**
- BETHANOCHOL-----(M)

Both methylation of choline & acetate replaced carbamate.

ALKALOIDS

- MUSCRINE
- PILOCARPINE

INDIRECT ACTING

Anti-cholinesterases

Reversible

CARBAMATES

- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium
- Rivastigmine
- Donepezil
- Galantamine
- Carbaryl
- Propoxur
-

Irreversible

ORGANOPHOSPHATES

- Parathion
- Malathion
- Sarin , Tabun,Soman (nerve gases)
- Dyflos
- Ecothiopate

Direct Acting Parasympathomimetics

Choline esters

- Acetylcholine (N+M) → Acetate + choline

- Bethanechol (M)
- Carbachol (N+M)
- Metahcholine (N+M)

→ Carbamate + choline

Alkaloids

- Nicotine (N)
- Muscarine (M)
- Pilocarpine (M)

CLINICAL USES

ACETYLCHOLINE

ACh has no therapeutic value because :

- ✓ **It has very brief duration of action i.e few seconds**
- ✓ **Diffuse action= as activates both N+M receptors**
- ✓ **Acetylcholine is a quaternary ammonium compound that cannot penetrate biological barrier**

ACH has nonspecific , diffuse actions which will lead to unwanted effects.

BETHANECHOL

The acetate with choline is replaced with Carbamate & Choline is methylated.

It is not readily destroyed by acetylcholinesterase enzyme because it cannot break the ester link between carbamate and choline. Since slowly degraded therefore, has a $t_{1/2}$ of 1 hour.

It cannot bind to nicotinic receptors as its choline is methylated.

CLINICAL USES OF BETHANECOL

BETH ACTIVATES BOWEL AND BLADDER

When there is non obstructive Urinary retention i.e

Postoperatively UR

postpartum UR

Spinal cord injury (neurogenic bladder),hypogenic bladder, myogenic bladdar

When there is Decrease GI motility i.e

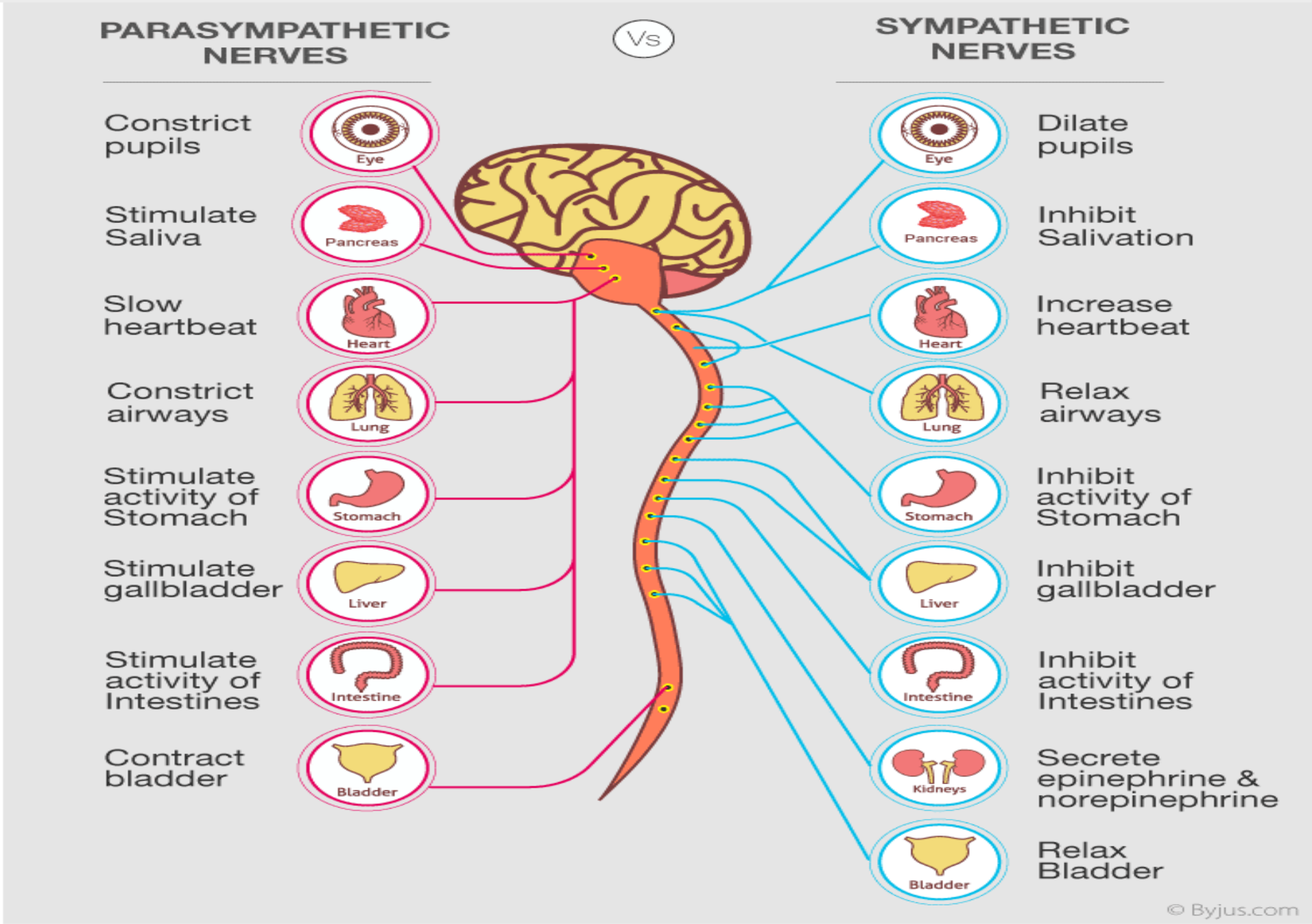
Post-op paralytic adynamic ileus

Gastro-paresis (Atonic stomach)

Congenital megacolon (part of colon is devoid of P.S innervation)

SIDE EFFECTS OF BETAHNECOL

GENERLIZED SIDE EFFECTS OF ACH



CONTRA INDICATIONS TO BETAHNECOL

Peptic ulcers
As it promotes HCL secretion so worsens the ulcers

COPD: As it causes broncho-constriction
&
Increases mucus secretions

IHD with Coronary insufficiency----MI
It causes vasodilation via M3 receptors on the endothelial cells.

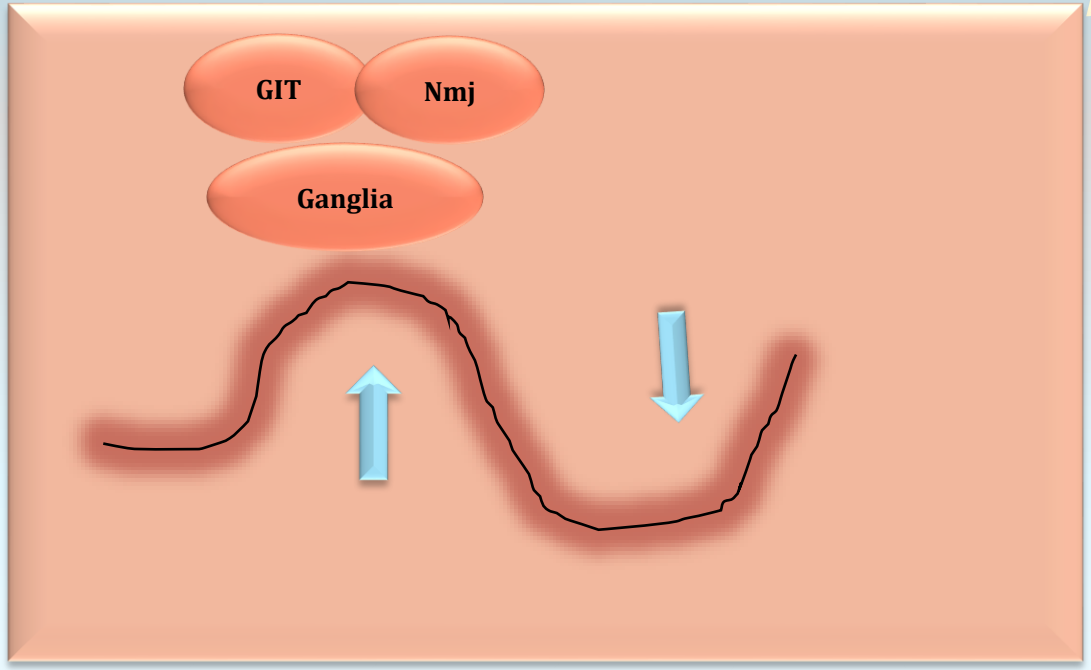
Hyperthyroidism as already there is atrial flutter or fibrilation

Parkinsons disease.
As it further deranges the balance between ACH and Dopamine

CARBACHOL

- CARBACHOL---------(M,N)
- Acetate repalaced by carbamate.

- It ahs very predominant action of the ganglia. Therefore not used systemically.



- First stimulates GANGLIA, GIT, NMJ then depress them

CARBACHOL CINICAL USES

Only used topically in the eye to cause meiosis thereby reducing the Intra Ocular Pressure.

For this purpose it is only used when Pilocarpine is ineffective

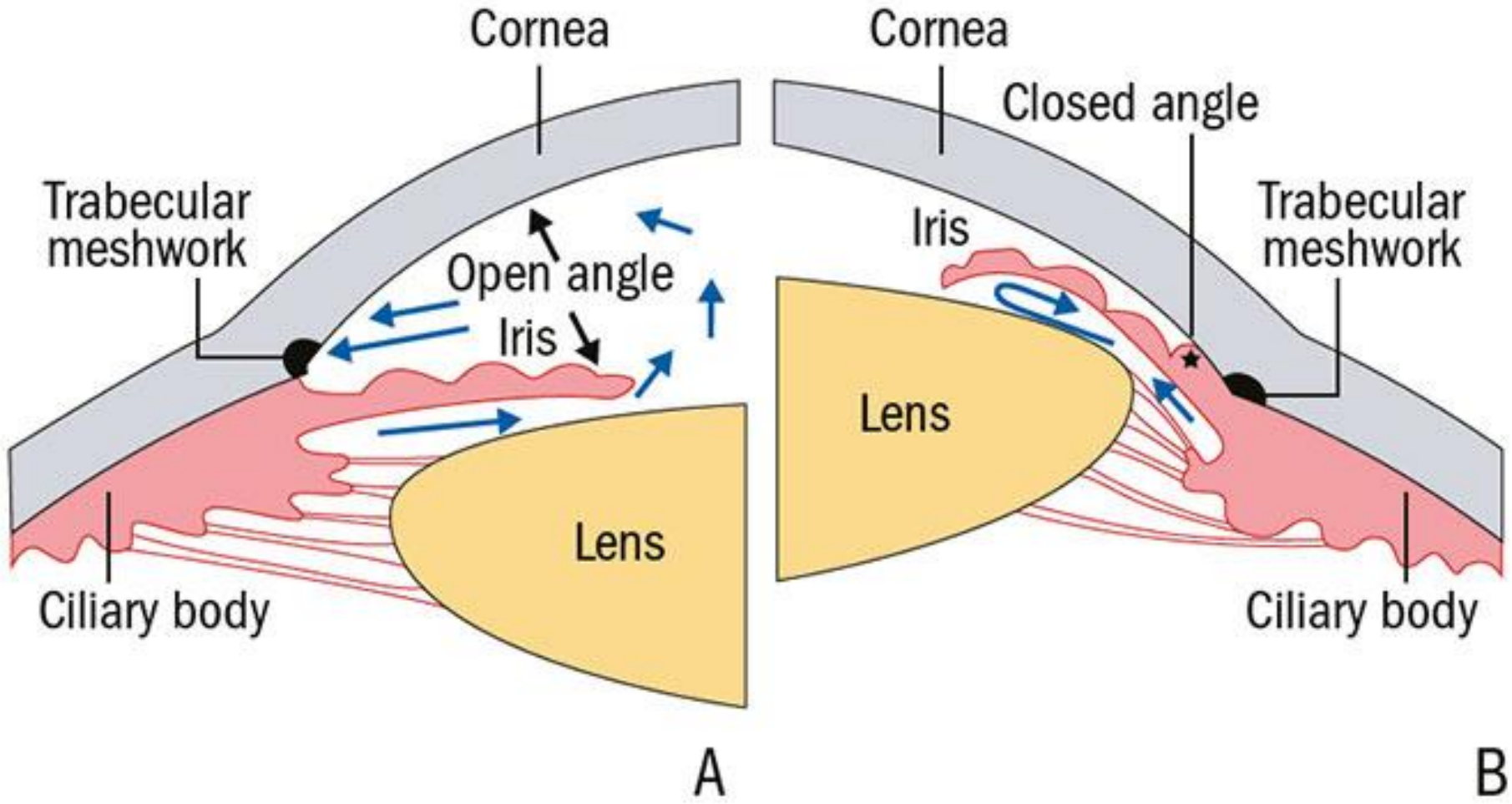
METHACHOLINE

- Use to check the hyper-reactivity of bronchial smooth muscles in asthmatic patients.
- Methacholine challenge ?

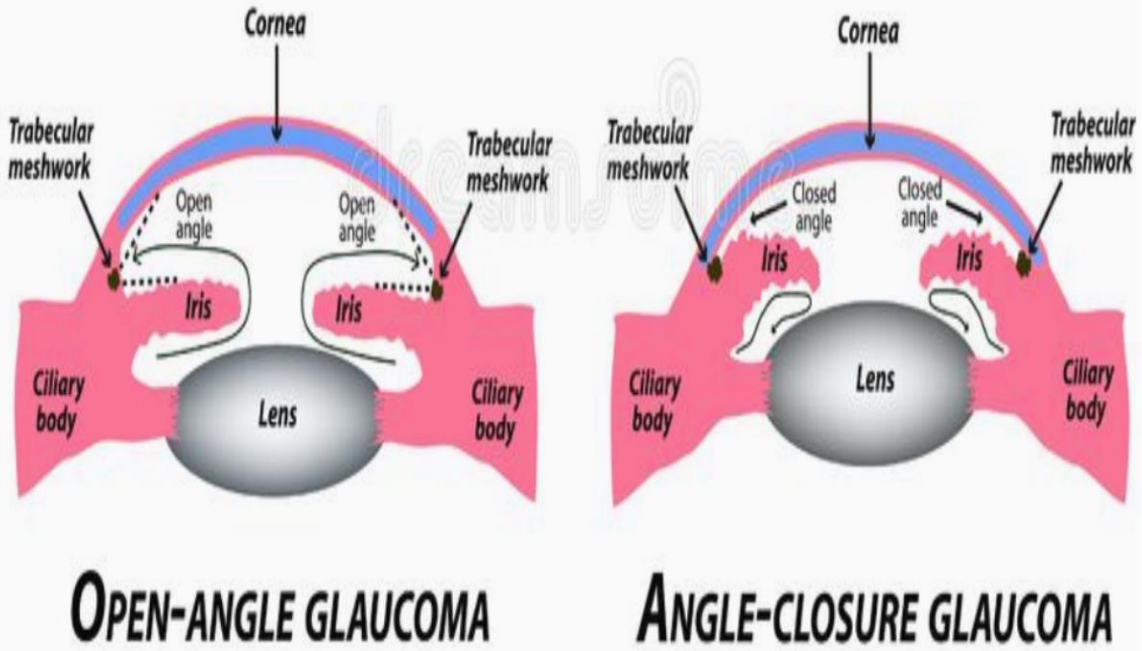
PILOCARPINE

Pilocarpine is a tertiary amine. It is stable against acetylcholinesterase.
It is basically an alkaloid derieved from a plant.

FIGURE 1 The anatomical and physiological differences between an open and narrow/closed anterior chamber angle



TYPES OF GLAUCOMA



OPEN-ANGLE GLAUCOMA

ANGLE-CLOSURE GLAUCOMA

In open angle glaucoma the irideocorneal angle is normal, the trabecular meshwork is hardened as a result of which the fluid has difficulty filter through it. This leads increased pressure in the anterior chamber.

In closed angle glaucoma either the anterior chamber is shallow or some has congenital narrow irideocorneal junction. In such people pupillary dilatation will further cause narrowing of the angle and further increase in the pressure in the anterior chamber.

Sometimes the pressure becomes so high that it starts accumulating in the post-chamber. Now this pressure in the posterior chamber further pushes the iris forward and further blocks the angle. This is associated with severe pain the eye, increased pressure in cornea may also develop. The eye may turn red.

ACUTE CLOSED ANGLE GLAUCOMA

Mechanism of action of Pilocarpine in relieving increased Intra Ocular Pressure

Closed angle glaucoma

Pilocarpine is instilled topically several times.
It act on the M3 receptors of sphincter pupilea.

Sphincter pupilea will contract and pull the base iris away from the angle, the angle will open.
This will lead to drainage of aqueous humor , thus decrease in IOP.

Open angle glaucoma

In open angle glaucoma atually the angle is open, the trabecular meshwork is hardened.

Pilocarpine is instilled topically. This will act on the M3 receptors of cillary muscles. The cillary muscle will pull the meshwork backward and open it. Thereby facilitating the drainage of aqueous humor and decreasing the IOP.

PILOCARPINE THERAPEUTIC INDICATIONS

- **Xero-stomia**
- **Sjogren syndrome**
- **After use of mydriatic agents**
- **Alternate use with mydriatic agent to break adhesions b/w iris and lens**
- **Glaucoma (topically)**

✓ **Glaucoma ?**

✓ **Open angle glaucoma ?**

✓ **Narrow angle glaucoma ?**

Drugs Used in Open-Angle Glaucoma

Drugs	Mechanism	Route of Administration
Cholinomimetics Pilocarpine, Physostigmine	Miosis & Ciliary muscle contraction, opening of trabecular meshwork; increased outflow	Topical
Beta-blockers Timolol, betaxolol, carteolol, levobunolol	Decreased aqueous secretion from the ciliary epithelium	Topical
Diuretics Dorzolamide (T) Brinzolamide (T) Acetazolamide (Oral)	Decreased aqueous secretion due to lack of HCO_3^-	Topical
Prostaglandins Latanoprost, bimatoprost	Increased outflow	Topical
Alpha-2 agonists Apraclonodine Brimonidine	Decreased aqueous secretion	Topical

INDIRECT ACTING PARASYMPATHOMIMETICS

Reversible

CARBAMATES

- Physostigmine
- Neostigmine
- Pyridostigmine
- Ambenonium

ALCOHOL

- Edrophonium

Irreversible (Organophosphorus compounds)

Insecticides

- Parathion
- Malathion
- Metrifonate
- DDT

War gases

- Soman

Others

- Echothiophate

INDIRECT ACTING PARASYMPATHOMIMETICS

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions.

Inhibitors of acetylcholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings.

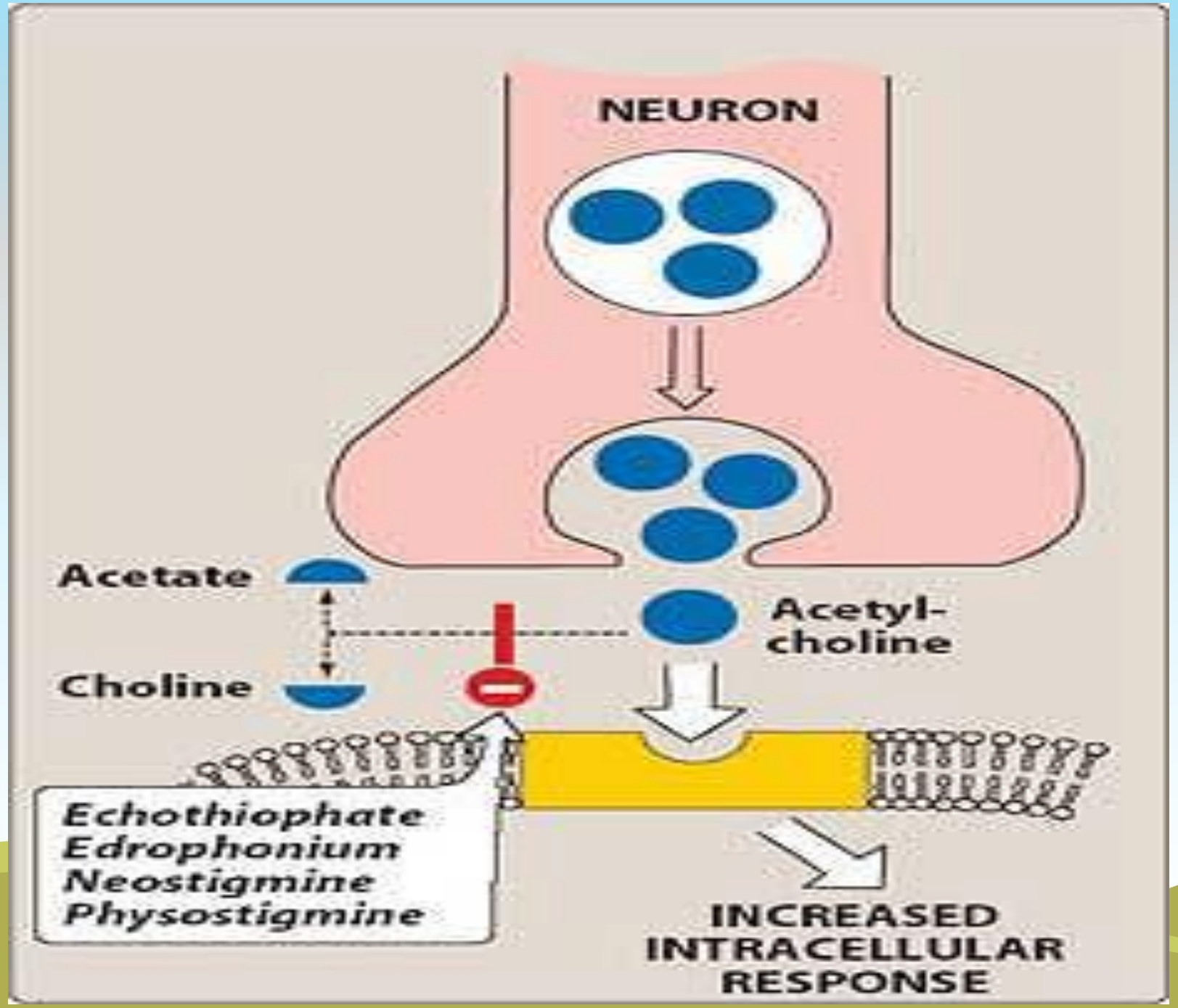
These drugs can thus provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the autonomic nervous system, as well as at neuromuscular junctions and in the brain.

REVERSIBLE

- **Physostigmine ⟶ (Alkaloid, Tertiary amine, less polar, can cross BBB, can cause CNS side effects)**

- **Neostigmine**
- **Pyridostigmine**
- **Ambenonium**
- **Edrophonium**

(Synthetic, Quarternary amine more polar can’t corss BBB, no CNS side effects)


NEURON
Acetate
Choline
Acetyl-
choline
Echothiophate
Edrophonium
Neostigmine
Physostigmine
INCREASED
INTRACELLULAR
RESPONSE

PHYSOSTIGMINE AND NEOSTIBMINE (CARBAMATES)

Make a labile covalent bond with anticholinesterase enzymes.

So inhibit the enzyme inhibits from 30 min – few hours)

EDROPHONIUM

Edrophonium is an alcohol derivative

It binds reversibly at the active site of Acetylcholinerterase enzyme preventing the hydrolysis of Acetylcholine.

It inhibits the enzyme for 10-20 minutes .

PHYSOSTIGMINE (Carbamate)

More lipid soluble so reach CNS , absorb via Fat and act on autonomic ganglia. And stimulate all the cholinergic effects.

CLINICAL USES

PHYSOSTIGMINE

It is Use in the treatment of :

- Overdose of anti-muscarinics like atropine, phenothiazines and TCA
- Urinary retention and Decrease GI motility like Bethanechol
- Glaucoma along with pilocarpine

Note :

Physostigmine is Lipid soluble, enters the central nervous system and reverses the central as well as the peripheral signs of muscarinic blockade

PHYSOSTIGMINE SIDE EFFECTS

PHYSOSTIGMINE SIDE EFFECTS

- OVER STIMULATION OF CNS
- At NMJ prolonged depolazation followed by paralysis
- Collapse of CVS
- Adverse effects due to overstimulation of all muscarinic reseptors

NEOSTIGMINE

NEOSTIGMINE = NO CNS ENTRY
Quaternary amine
Cant cross the BBB
Less fat soluble so very little effect on ganglia and post synaptic parasympathetic neuro effector stimulation will be less.

It is Use in the treatment of :

- Myasthenia gravis
- Eaten lambert syndrome
- Urinary retention and Decrease GI motility like Bethanechol and physostigmine

Myasthenia Gravis

- Autoimmune disease
- Affecting skeletal muscle NMJ
- Antibodies are produced against Ach Nicotinic receptor-channel complex
- Decreases the number of receptors
- Leading to impairment of N.M transmission

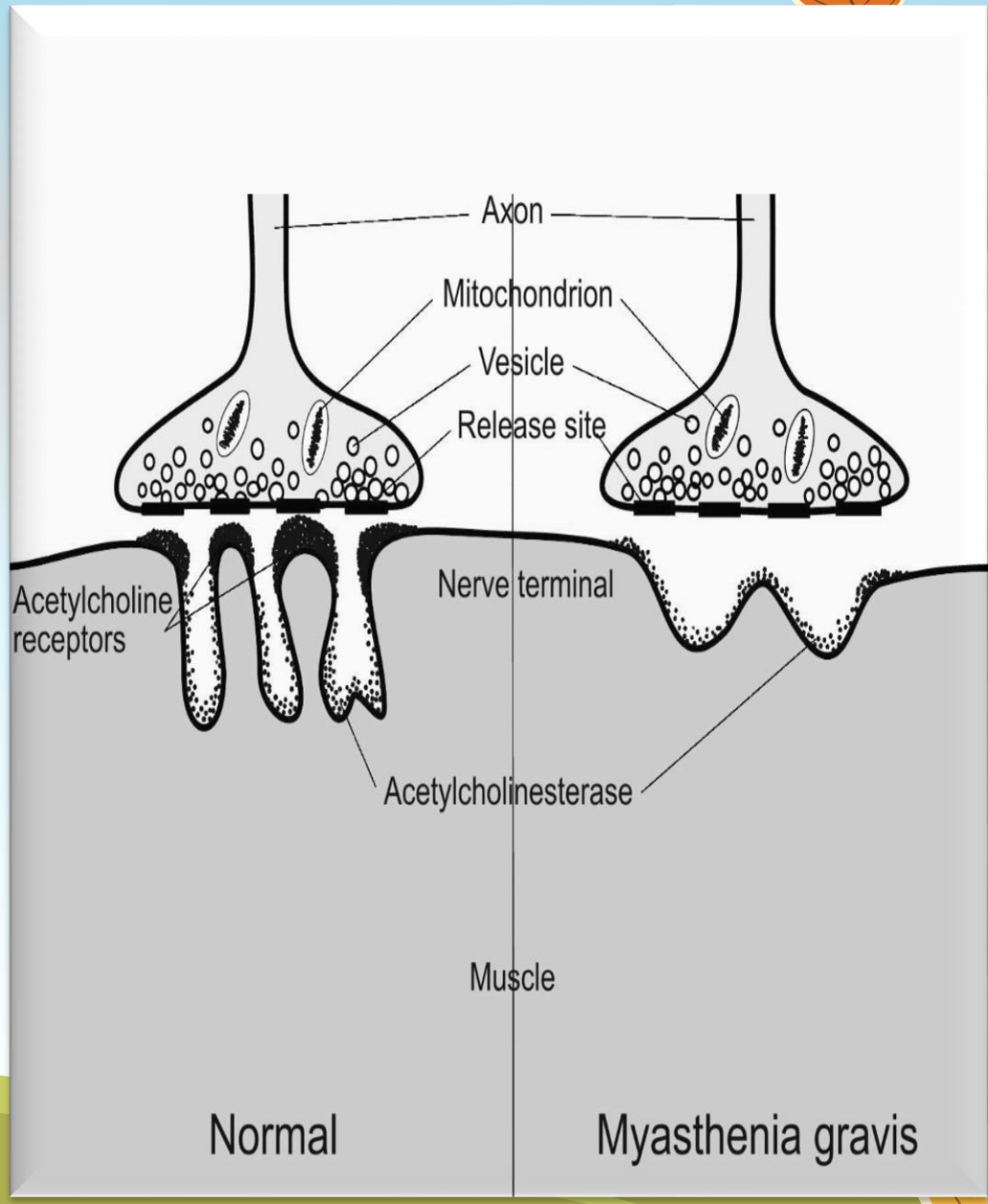
Sign & Symptoms

Ptosis

Diplopia,Difficulty in speaking and swallowing

Weakness of arms and legs

Severe disease may affect all the muscles, including respiratory muscles



PYRIDOSTIGMINE/AMBINOMIUM

P = Prolonged duration of action

Similar uses as that of physostigmine and neostigmine but it has got long duration of action so prefer in chronic diseases

EDROPHONIUM

eDro = diagnosis, differentiation
Phony = fake / short

Edrophonium is very short acting cholinesterase inhibitor=10-20 mints

Edrophonium is used:

- In the Diagnosis of myasthenia gravis
  - ✓ 2 mg dose is injected IV after baseline muscle strength has been measured
  - ✓ If no reaction occurs after 45 seconds, an additional 8 mg may be injected
  - ✓ If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5 minutes can usually be observed
- To differentiate myasthenia crisis from cholinergic crisis

Cholinergic crisis

- Overuse of acetylcholinesterase inhibitors in Mysthenia Gravis→ ↑↑ Ach

Myesthenia crisis

- Underuse of drugs in Mysthenia Gravis →↓↓ Ach

In both cases muscle weakness occurs so Edrophonium is used to differentiate between two.

If patient has myesthenia crisis, the strength of muscles will improve

In cholinergic crisis, patients become paradoxically weak because of nicotinic depolarizing blockade of motor end plate

Irreversible

- **ORGANOPHOSPHORUS COMPOUNDS**

- All are highly lipid soluble
- They are rapidly absorbed from intact skin, mucosal surfaces and GIT, and cross BBB.
- **They inhibit Ach Esterase irreversibly, covalently bind to its active site**
- Recovery depends on synthesis of new enzyme

Organophosphorus Poisoning

- Farmers
- Suicide / Accidental / Homicide (Rat killing tablets)

Treatment

GENERAL MEASURES:

- Clothes and Dermal decontamination, gastric lavage
- Artificial respiration & suctioning of secretion
- Supportive treatment

SPECIFIC MEASURES:

Atropine

- Ach Antagonist= reverse symptoms

Pralidoxime (cholinesterase reactivator)

- Pralidoxime breaks the bond b/w phosphate group of organophosphorus compound and cholinesterase, thus reactivating the enzyme.

AGING :

It is basically a chemical stabilization of bond b/w phosphate group of organophosphorus comp and serine group of AChE which occurs over time, after the release of alkyl group of organophosphorus compound. Once aging occurs then its impossible for Pralidoxime, to break the bond between the remaining drug and the enzyme.

Therefore Pralidoxime must be given within 24 hrs after poisoning.

Alzheimer's disease

Most common form of dementia

- Diagnosed in people over 65 years of age
- Difficulty in remembering recent events
- Confusion irritability and aggression
- Trouble with language
- long-term memory loss
- Gradually, bodily functions are lost, ultimately leading to death
  - **Caused by reduced synthesis of the Ach in brain**

Acetylcholinesterase inhibitors

- Rivastigmine, Galantamine ,Tacrine ,Donepezil

Adverse Effects Cholinergic Drugs

Muscarinic Manifestation

(DUMBBLES)

- Diarrhea, abdominal pain
- Urination
- Miosis, pin point pupil
- Bradycardia
- Bronchospasm
- Lacrimation
- Emesis
- Salivation

Nicotinic Manifestations

- Muscle Fasciculations & Cramps
- Increase Adrenal Medulla activity= Tachycardia, palpatations and Hypertension

CNS Manifestations

- Anxiety, restlessness, confusion, coma
- Depression of respiratory & CVS centers, death finally