AUTONOMIC NERVOUS SYSTEM

Learning objectives

1. Few points about the physiology of autonomic nervous system
2. Acetylcholine as a transmitter of parasympathetic system, its synthesis and release
3. Classification of cholinergic receptors, their location and the pharmacological actions induced by their stimulation
4. Classification of cholinergic drugs
5. Organophosphorus poisoning
6. Classification of anti-cholinergic drugs
7. Atropine as a prototype of anti-muscarinic drugs

Autonomic nervous system

It is an independent system i.e. its activities are not under direct control, it includes:

1. Sympathetic (thoracolumbar) division
2. Parasympathetic (craniosacral) division

Both divisions originate in nuclei within CNS and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia.

*Almost all efferent fibers leaving CNS are cholinergic.

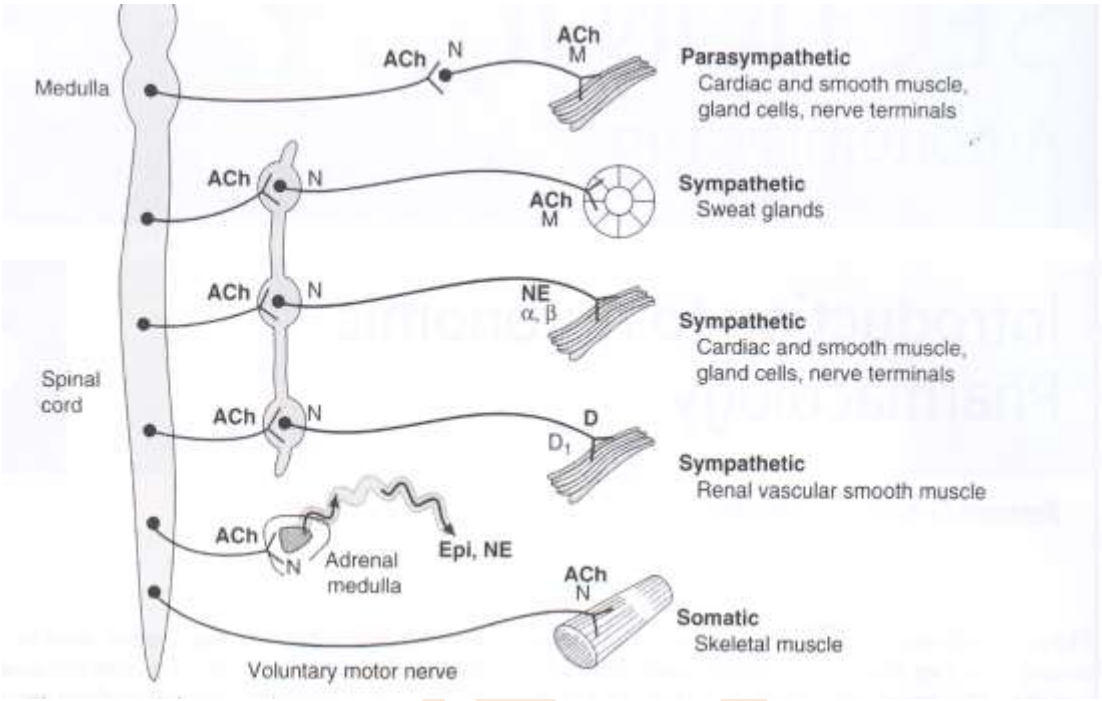
*All preganglionic efferent autonomic fibers and the somatic (non autonomic) motor fibers to skeletal muscles are cholinergic.

*Most parasympathetic postganglionic & few sympathetic postganglionic fibers are cholinergic.

*Most postganglionic sympathetic fibers release noradrenaline so are adrenergic.

*Dopamine is a very important transmitter in CNS & there is evidence that it may be released by some peripheral sympathetic fibers.

*Adrenal medullary cells (an embryological analogue to postganglionic sympathetic neurons) release a mixture of adrenaline & nor-adrenaline.



PARASYMPATHETIC SYSTEM

Acetylcholine (Ach) is a wide spread chemo transmitter in the body mediating a broad range of physiological effects.

Synthesis & release

Ach is synthesized in the cytoplasm from

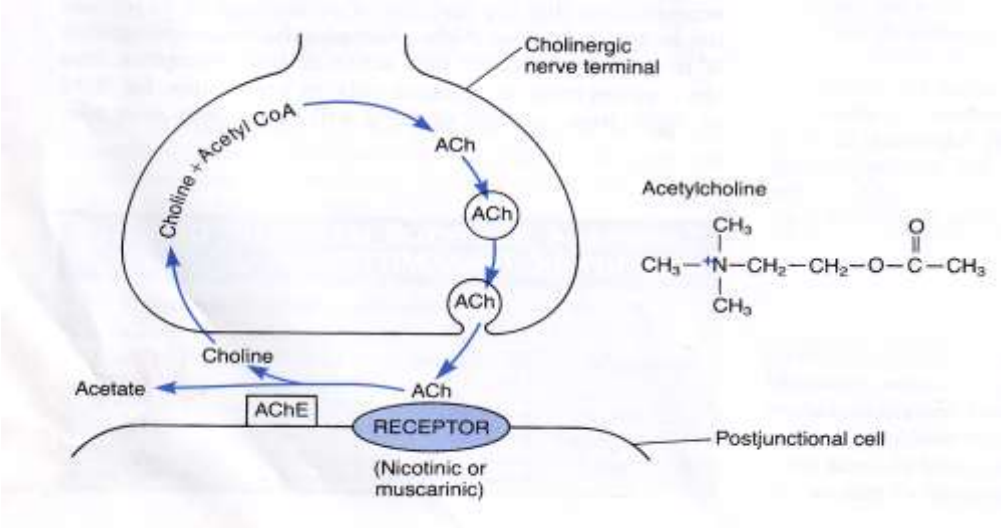
Acetyl CoA + Choline $\xrightarrow{\text{ChAT(choline acetyl transferase)}}$ **Ach**

Once synthesized, Ach is stored in vesicles & then released in response to action potential.

*After release from presynaptic terminal:

1. Ach binds to & activates receptors located in post junctional cells (cholinoceptors).
2. Ach is destroyed by cholinesterase which splits Ach to choline & acetate (neither of each has significant transmitter effect)

*choline is taken up into the cholinergic nerve terminal.



*Most cholinergic synapses are richly supplied with cholinesterase so half-life of Ach is very short (seconds).
*Cholinesterase enzyme is of 2 types:
1. True- found at cholinergic nerve endings & in RBCs
2. False (pseudo cholinesterase)-has a lower specificity for Ach & is found in blood plasma, liver & many other tissues.

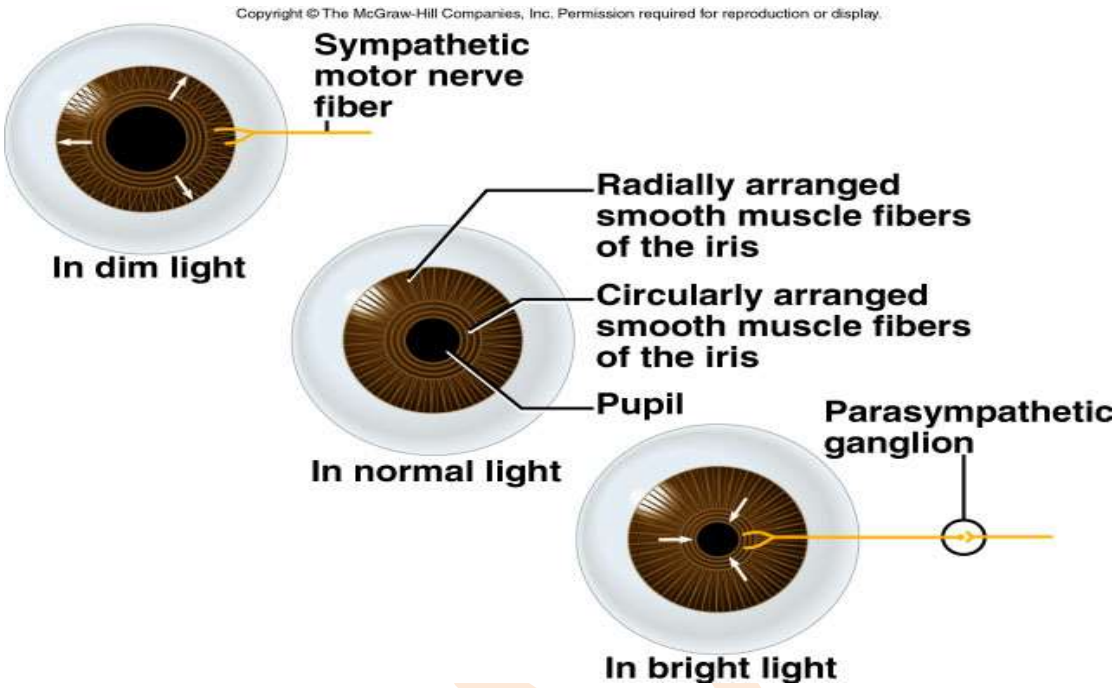
Mechanism of action

There are 2 distinct classes of receptors for Ach defined on the basis of their activation by alkaloids:
1. Muscarinic receptors (activated by muscarine) which are of 5 subtypes:
   a. M_1- in gastric parietal cells
   b. M_2- in heart, nerves, smooth muscles
   c. M_3- in exocrine glands, smooth muscles and bladder
   d. M_4 &M_5-in CNS
2. Nicotinic receptors (activated by nicotine) - are found at neuromuscular junctions and their stimulation causes muscle fasciculation.

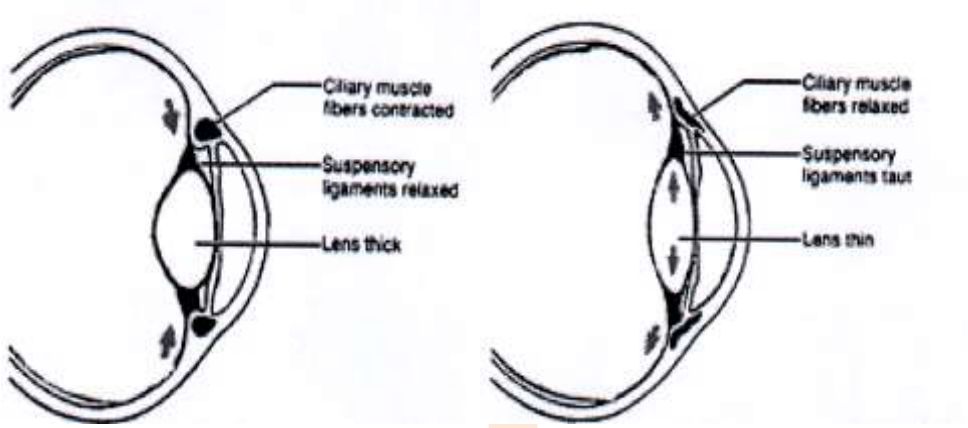
Muscarinic receptors are found in the following sites:

A. Smooth muscles

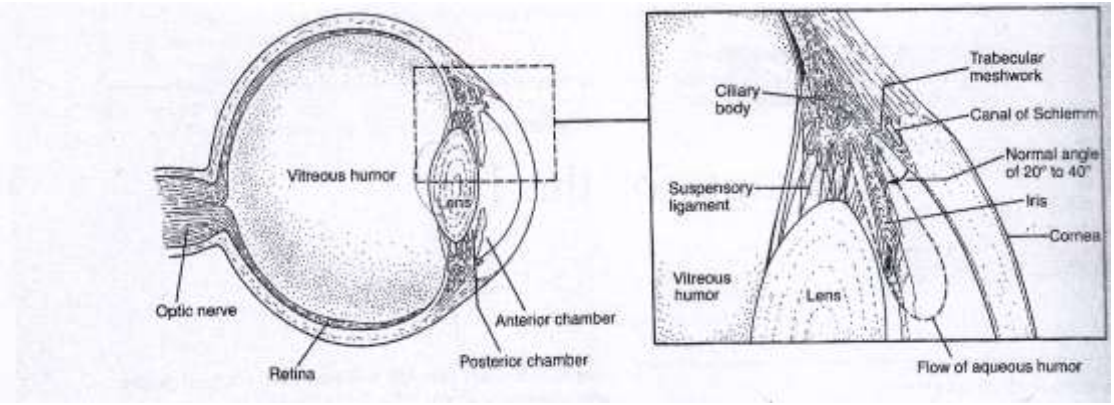
a. Eye- stimulation of the receptors causes miosis due to contraction of circular muscle of the iris (constrictor pupillae).



The eye is also accommodated for near vision due to contraction of ciliary muscle



Intra-ocular pressure also falls by:
1. Miosis- the iris is pulled away from the angle of the anterior chamber
2. Contraction of ciliary muscle, the trabecular meshwork, on the base of the ciliary muscle, is opened)
Both these effects facilitate aqueous humor flow into canal of schlemm.



b. Bronchi- bronchoconstriction & mucosal hyper secretion

c. Gastrointestinal tract (GIT)- stimulation causes:
* increased motor & secretory activity of the gut and may cause colicy pain.
*increased exocrine secretions mainly of salivary & gastric glands while pancreas & small intestinal glands are less stimulated.
*Relaxation of sphincters- anal sphincter (causes defecation)
- esophageal sphincter (causes regurgitation)

d. Genitourinary tract (GUT)
Contraction of detrusor muscle, relaxation of trigone & sphincter's muscles which promote micturition.

B. Exocrine glands- increased secretions mainly of salivary, lachrymal, bronchial & sweat glands.
Sweat glands are cholinergic, although anatomically are part of sympathetic system, axillary sweat glands are adrenergic.

C. Cardiovascular system (CVS)- (effects are through M_2 receptors)
Stimulation causes bradycardia and AV block. It also causes vasodilatation and lowering of blood pressure by indirect mechanism through releasing of nitric oxide.

Note
Both muscarinic & nicotinic receptors are found in the central nervous system (CNS) and causing stimulation followed by depression.

Cholinergic drugs (Parasympathomimetic drugs) include:

1. Directly acting (act directly at cholinergic receptors) including:
   a. cholinesters
   b. alkaloids
2. Indirectly acting drugs (cholinesterase inhibitors- influence cholinergic receptors indirectly by preventing the breakdown of Ach including:
   a. reversible anti-cholinesterases
   b. irreversible anti-cholinesterases

I. Directly acting drugs

A. Cholinesters

1. Acetyl choline – is a substance with huge variety of effects on both muscarinic & nicotinic receptors and is rapidly destroyed in the body, so is unlikely to be useful when given systemically.

2. Carbachol & Bethanecol

Are not destroyed by cholinesterase, their actions are more pronounced on the bladder & GIT, so are used to stimulate these organs e.g. after surgery.

B. Alkaloids

a. Nicotine- is absorbed through mucous membranes. Its $t_{1/2}$ is 2h, is metabolized by CYP450.

*In large doses- acts at autonomic ganglia & voluntary neuromuscular junction causing paralysis. CNS is first stimulated (causing vomiting, tremor, convulsion) & followed by depression.

***clinical use-** is a social drug used as an adjunct to stopping its own abuse as tobacco.

b. Muscarine- is of no therapeutic use.

*it has a role in discovery of cholinergic receptor subtypes

*has a toxicological significance because of its presence in certain poisonous mushrooms.

c. Pilocarpine

Is a direct acting muscarinic agonist, also stimulates then depress CNS

Clinical uses

1. Glaucoma , it decreases IOP by miosis & contraction of ciliary muscle

2. is used orally for treatment of xerostomoia (dry mouth) following irradiation of head & neck tumors

Adverse effects -decreased visual acuity, local irritation& eye pain, rarely is absorbed in amounts sufficient to cause systemic effects (bradycardia, bronchospasm, hypotension, urinary urgency, diarrhea, hyper salivation & sweating)

*It should be cautiously used in patients with bronchial asthma or bradycardia

*Its systemic toxicity is reversed by atropine

*It is available as a solution (eye drops) 0.25-10%, a gel (4%)

II. Indirectly acting drugs

They are cholinesterase inhibitors (Anticholinesterases) that prevent degradation of Ach by cholinesterase, are of 2 types:

1. Reversible- produce effects of moderate duration
2. Irreversible- produce long lasting effects

A. Reversible inhibitors

a. Neostigmine ($t_{1/2}$=2h)

Is a synthetic reversible anticholinesterse whose action is more prominent on neuromuscular junction.

It contains quaternary nitrogen atom, so it is poorly absorbed after oral administration and it cannot readily cross membranes including of GIT, BBB & placenta.

Pharmacological effects- intensifies transmission at all junctions where Ach is a transmitter

Pharmacokinetics can be administered orally, s.c, i.m, i.v, duration of action is 2-4 h, cannot cross BBB, eliminated by enzymatic degradation.

Is used in myasthenia gravis

b. Physostigmine is similar to neostigmine, but is not quaternary ammonium compound, so can readily cross membranes like BBB.

Uses

1. is drug of choice in treatment of atropine poisoning because it can cross BBB & reverse muscarinic blockade in CNS
2. glaucoma

c. Pyridostigmine is similar to neostigmine, but has less powerful action that is slower in onset & slightly longer in duration.

It is **used in** myasthenia gravis.

d. Edrophonium is structurally related to neostigmine but its action is brief.

Uses a. diagnosis of myasthenia gravis
b. to differentiate between myasthenic crisis (is improved) and cholinergic crisis (is aggravated)

***A more recent use of anticholinesterase drugs is to improve cognitive function in patients with Alzheimer's disease like: Donepenezil, galantamine, rivastigmine.**

Myasthenia gravis

Is an autoimmune disease where there is impairment of synaptic transmission at NMJ, 85% of patients have raised titer of auto Abs to the nicotinic Ach receptors. These Abs accelerate receptor turnover, shortening their life time in skeletal muscle membrane from 7 days to 1 day in myasthenic patients.

Clinical features diplopia, fatigue, ptosis, difficulty in speaking & swallowing.

Diagnosis

1. Edrophonium i.v, will dramatically & transiently relieve myasthenic muscular weakness.
2. Measurement of Ach receptor Abs titer to confirm diagnosis.

Treatment

Anticholinesterase drugs, pyridostigmine is preferred because its action is smoother than neostigmine.

Neostigmine has more rapid onset of action so has an advantage to be given in the morning to get the patient mobile.

*These drugs are given orally, but can be given parenterally if there is difficulty of swallowing.

B.Irreversible cholinesterase inhibitors

Are highly toxic, employed primarily as insecticides. They are also developed, to be used in war called as nerve gases but they are volatile liquids.

They are organophosphate cholinesterase inhibitors because they contain an atom of phosphorus. They are highly lipid soluble so are readily absorbed from all routes of administration like skin, GIT &

inhalation. Once they are absorbed, they have readily access to all tissues & organs including CNS.

Mechanism of action

They bind irreversibly to the active center of cholinesterase so preventing the enzyme from hydrolyzing Ach. Because of irreversible binding, effects persist until new molecules of cholinesterase are synthesized.

Typical features of acute poisoning

1. GIT-salivation, vomiting, abdominal cramps, diarrhea, involuntary defecation
2. Respiratory system-bronco-constriction, increased bronchial secretions, cough, wheezing & dyspnea
3. CVS-bradycardia
4. GUT-involuntary micturition
5. Skin- sweating
6. Skeletal system- muscle weakness & twitching
7. CNS- miosis, anxiety, headache, convulsions, respiratory failure

***death is due to respiratory failure (action in CNS causing respiratory muscle paralysis) & due to excessive bronchial secretions & bronco-constriction.**

Treatment

1. contaminated clothes should be removed & skin washed
2. atropine 2mg i.m or i.v & repeated every 15-60 min until dryness of mouth & heart rate exceeding 70 beats/min which indicates adequate effect
3. mechanical ventilation
4. diazepam for convulsions
5. atropine eye drops to relieve headache caused by miosis
6. enzyme reactivation- pralidoxime reverses poisoning by dissociating organophosphate inhibitors from the active center of cholinesterase. It is given by a slow i.v injection over 5-10 min.

*Its efficacy is greatest if administered within the first 12 hrs of poisoning, if significant reactivation occurs, muscle power improves within 30 min.

*It cannot cross BBB, so cannot reverse cholinesterase inhibition in CNS.

Anticholinergic drugs

They are divided into:
1. Antimuscarinic drugs (atropine related drugs) act principally at postganglionic cholinergic (parasympathetic) nerve endings
2. Antinicotinic drugs: a) ganglion-blocking drugs
b) neuromuscular blocking drugs

I. Antimuscarinic drugs (parasympatholytic drugs)

A. Atropine (belladonna alkaloid)

Is the prototype of this group, is an alkaloid from the deadly night shade *Atropa belladonna*.

Mechanism of action

It competitively & selectively blocks muscarinic receptors at therapeutic doses, but in sufficiently high doses, it produces some blockade of nicotinic receptors as well.

Pharmacological effects

a. Exocrine glands-all secretions, except milk, are diminished. Dry mouth & dry eye are common. Gastric acid secretion is reduced as well as the volume of gastric secretion, so PH is little altered. Sweating is inhibited, bronchial secretions are reduced & become viscid as removal of secretions by cough & ciliary action is rendered less effective.
b. Smooth muscles are relaxed, decreased tone & peristalsis in GIT, bronchodilatation, decreased micturition & urinary retention may be induced especially in preexisting prostatic enlargement.
c. Ocular effects mydriasis with increased IOP, accommodation for far vision due to paralysis of ciliary muscle (cycloplegia).
d. CVS reduces vagal tone, so causes tachycardia & enhanced conduction in bundle of His, has no significant effect on peripheral blood vessels in therapeutic doses but in overdose causes marked vasodilatation.
e. CNS causes mild CNS stimulation at therapeutic doses, in toxic doses it causes hallucination & delirium, extremely high doses result in coma, respiratory arrest & death.
*atropine is readily absorbed from GIT, can be given orally, topically & injection.

Clinical uses

1. preanesthetic medication
2. in ophthalmology
3. bradycardia following myocardial infarction
4. cholinergic poisoning

Adverse effects dry mouth, blurred vision & photophobia, increased IOP, urinary hesitancy or urinary retention, constipation, anhidrosis (deficiency or absence of sweat) & hyperthermia, thickening & drying of bronchial secretions resulting in bronchial plugging.

Contraindications

1. Glaucoma
2. Prostatic hypertrophy
3. Patients with tachycardia
4. Intestinal atony

Atropine poisoning

Is characterized by dry mouth, blurring of vision, photophobia, hyperthermia, CNS effects (hallucination & delirium), hot dry & flushed skin.

*death results from respiratory depression secondary to blockade of cholinergic receptors in brain.

Treatment

1. minimizing absorption- by syrup of ipecac to induce vomiting, & activated charcoal to adsorb the poison within intestine
2. Antidote- physostigmine, because it crosses BBB.

B. Hyoscine (scopolamine)

Is structurally close relative to atropine.

*The main difference: a. is CNS depressant, causes confusion esp. in elderly
b. mydriasis is briefer than atropine
c. suppresses emesis & motion sickness

C. Hyoscine butylbromide (Buscopan)

Also blocks autonomic ganglia. If injected, it is effective relaxant of smooth muscles including cardia, pyloric antral region & colon. So is useful in colic & endoscopy.

D. Homatropine
Is used as eye drops , its action is shorter than atropine, so less likely to cause serious increased IOP, the effect wears off in a day or two.

E. Tropicamide (Mydriacyl) & Cyclopentolate (Mydrilate)
Are used as eye drops for mydriasis & cycloplegia, are quicker & shorter acting than homatropine, produce mydriasis within 10-20min & duration of action is 4-12h.

F. Ipratropium (Atrovent)
Is used as an inhaled bronchodilator for acute bronchial asthma & chronic obstructive pulmonary disease.

G. Flavoxate (Urispas) & Oxybutynin (Cystrin)
Is used for urinary frequency, tenesmus, urgency incontinence because it increases bladder capacity & reduces unstable detrusor contractions.

H. Propantheline (Pro-Banthine)
Is used as smooth muscle relaxant e.g. in irritable bowel syndrome & diagnostic procedures.

I. Benzhexol & Orphenadrine used in parkinsonism.

J. Promethazine is used as an antiemetic.

II. Ganglion-blocking drugs

They have limited applications because they lack selectivity, so their only use is to lower blood pressure & only in special circumstances.
E.g.
Mecamylamine (Inversine) is the only available drug in USA

Short essay questions

1)Write shortly on the pharmacological effects of Ach on:
a.Eye
b.GIT

2)What are the clinical uses of pilocarpine?

3)a.What are the contraindications to the use of atropine?
b.What are the differences between atropine and hyoscine?

MCQ

1)Stimulation of muscarinic receptors causes
T a.relaxation of anal sphincter
F b.mydriasis
F c.tachycardia
F d.urinary retention
T e.excessive salivation

2)Atropine
F a.is used in patients with tachycardia
F b.opposes mucarinic & nicotinic effects of acetyl choline
T c.increases intra ocular pressure
T d.its poisoning is treated by physostigmine
T e.is contraindicated in prostatic hypertrophy

3)Physostigmine
F a.is a quaternary ammonium compound
T b.is drug of choice in atropine poisoning
F c.is contraindicated in glaucoma
F d.is an irreversible cholinesterase inhibitor
T e.can cross BBB