PARASYMPATHOMIMETICS

Cholinergic receptors:

These receptors respond to Ach and its analogues. They are subdivided into: •

1-Muscarinic receptors:

respond to Ach They are present on the surface of the effector cells of heart, endothelium of blood vessels, smooth muscles, presynaptic nerve terminals & exocrine glands. There are several subtypes of muscarinic (M) receptors e.g. M1, M2, M3 – etc. these receptors are generally blocked by **atropine**

2-Nicotinic receptors:

respond to nicotine (another Ach analogue) there are two major subtypes:

- Nn type :present in all autonomic ganglia and blocked by ganglion blockers.
- Nm type :present in the motor end plate of skeletal muscles an blocked by curare.

:

Receptor type	Molecular transduction mechanism	Physiological action
M_1 muscarinic	Increase inositol triphosphate(I_3P) and diacylglycero(DAG)	**-CNS stimulation Smooth muscle contraction -Increase release of endothelial derived relaxation factor and gastric HCL**
M_2 muscarinic	Decrease cAMP	**-Decrease all cardiac properties except atrial conductivity.by inhibition of S.A node .No direct effect on ventricular muscels. -Precynaptic inhibition of release of acetylcholine and other neurotransmitters**
M_3 muscarinic	Like M_1	**-Smooth muscle contraction in muscles of the wall of GIT and urinary tract ,bronchi ,uterus and blood vessels -Increase release of all digestive juices and respiratory secretions**
M_4	Like M_2	**Precynaptic inhibition of neurotransmitter release**
M_5	Like M_1	**CNS stimulation**
Nm nicotinic musclular	Increase intracellular sodium	**Increase skeletal muscle contraction**
Nn nicotinic neural	**Increase intracellular sodium**	**-CNS stimulation. -Increase adrenaline secretion from suprarenal gland. -Stimulation of autonomic ganglia**

- **Molecular mechanism o(muscarinic receptors stimulation:**
- 1- G - protein - coupling of M_l – M_3 to phospholipase C , leading to the release of second messengers, Diacylglycerol (DAG) and Inositol triphosphate (IP3) .
- a- DAG modulates the action of protein kinase C , an enzyme important in secretion.
- b- IP3 evokes the release of calcium from intracellular storage sites,
- resulting in contraction of smooth muscles.
- 2- Coupling ofM2 to adenyle cyclase through the inhibitory G- protein.
- 3- Coupling of muscarenic receptors directly to potassium channels in the heart and elsewhere . Muscarenic agonists facilitate opening of these channels

INTRODUCTION (Rest and digest)

Parasympathomimetics or cholinergic drugs are drugs that produce parasympathetic like actions •

because it works in time that body need to rest

Actions of parasympathomimetics are •

CVS: »

1- Decrease in heart rate and cardiac output:

2- Decrease in blood pressure: causes vasodilation and lowering of blood pressure by an indirect mechanism of action. Acetylcholine activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide.Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation.

blood vessels isn't parasympathetic innervation

Ach → production of nitric oxide → stimulate smooth muscle → smooth muscl relax

EYES:

1- stimulating ciliary muscle contraction for near vision

2- constriction of the pupillae sphincter muscle causing miosis (marked constriction of the pupil)

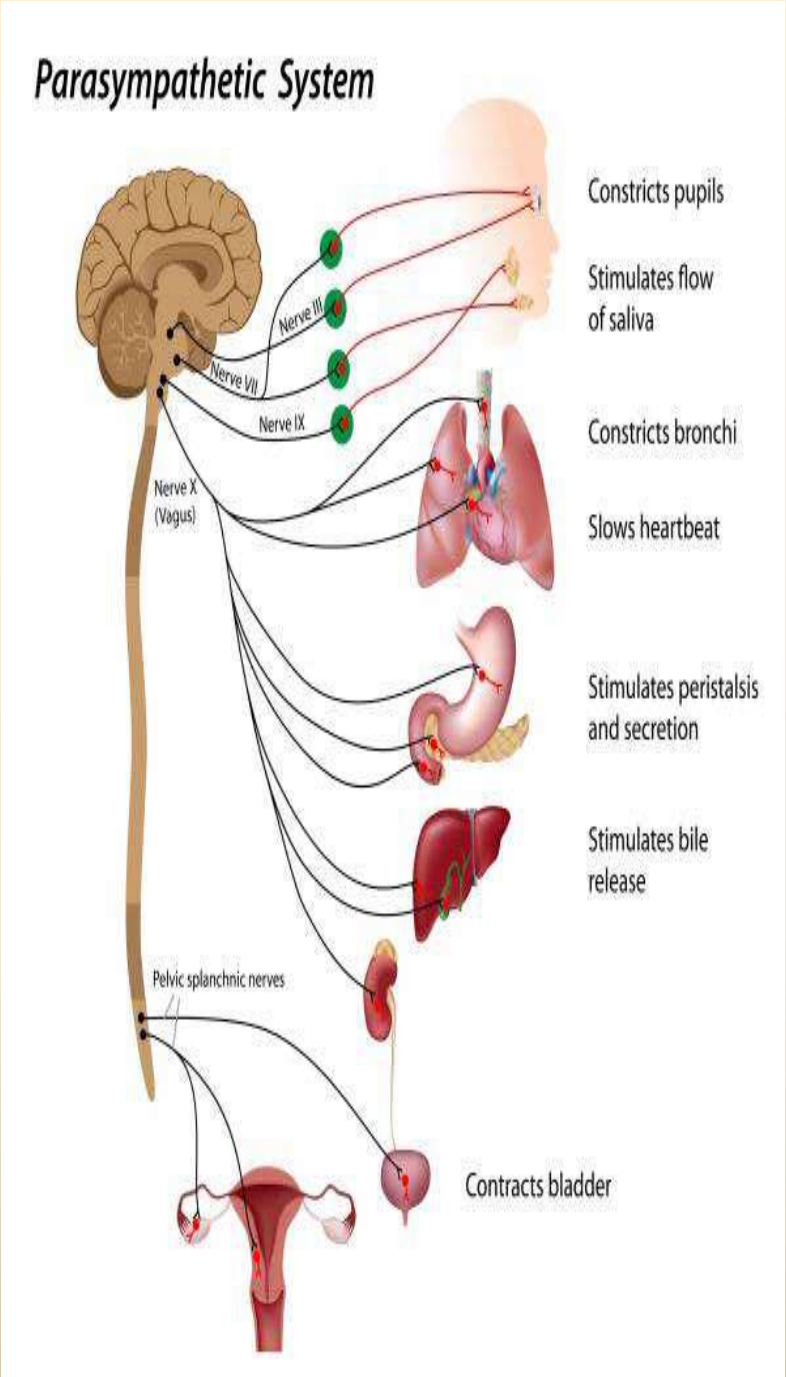
3- stimulate tears

4- Reduction of intraocular pressure (IOP)

Bronchi: bronchoconstriction

GIT: increases salivary secretion and stimulates intestinal secretions and motility

In the genitourinary tract: increased the tone causing expulsion of urine



Cholinergic agents adverse effects

- Bradycardia and hypotension.
- Miosis, lacrimation, salivation, sweating
- Urgency and spontaneous micturition
- Bronchospasm and increased bronchial secretion.
- Colic, vomiting, diarrhea, hyperacidity & peptic ulcer

General contraindication of parasympathomimetics → موانع الاستعمال

- Bradychardia, heart failure, heart block
- Bronchial asthma
- Peptic ulcer
- Parkinsonism → no balance in Ach and dopamin
- Mechanical obstruction of the GIT and urinary bladder

high → that can cause high contraction

Actions related to stimulation nicotinic receptors

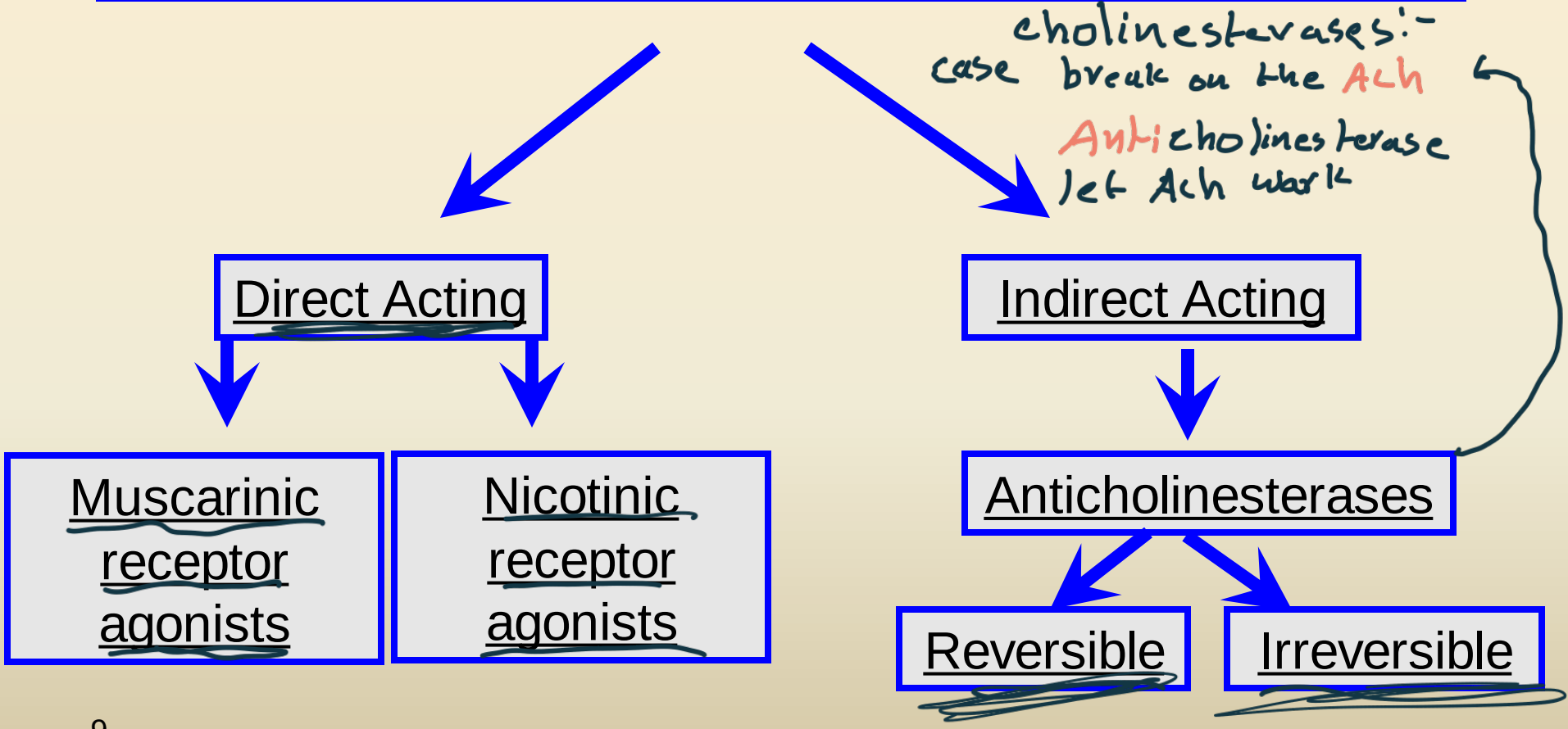
++of Nm: skeletal muscle twitches -

++ of Nn: in autonomic ganglia & adrenal gland so increase -

adrenaline &NA so hypertension in atropinized dogs

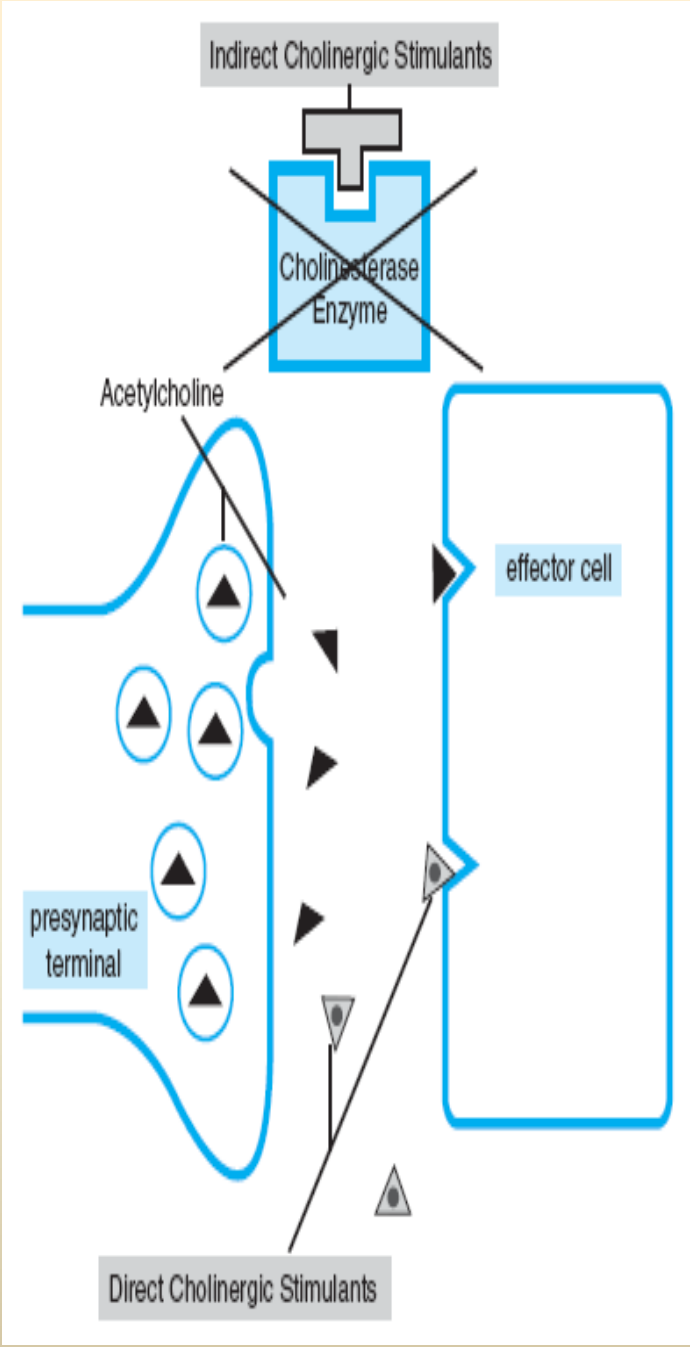
PARASYMPATHOMIMETICS (CHOLINOMIMETICS):

Drugs that facilitate or mimic some or all of the actions of the parasympathetic nervous system.



Parasympathomimetics are classified according to the mechanism of action into:

- Direct Parasympathomimetics: **-choline esters**
  -alkaloid
- Indirect Parasympathomimetics (**Anti-cholinesterases):-reversible**
  -irreversible
- Direct Parasympathomimetics: They stimulate the muscarinic receptors directly.
- Indirect Parasympathomimetics (Anti-cholinesterases): They inhibit cholinesterase enzyme leading to accumulation of endogenous acetylcholine at both muscarinic and nicotinic receptors



Choline esters

→ The name and the kind of receptor (N or M)

	Acetyl choline	methacholine	bethanicol	Carbachol
GIT absorption	No	partial	compelete	
fate	By true and pseudo ch E	By true only	Not	
duration	transient	long	Longer	
Actions: 1-nicotinic	+	-	-	+
2-muscrinic	+	+	+	+
3-selectivity	**Non selectivity**	**heart**	**GIT,urinary**	**eye,GIT,urinary**
uses	Not used	-Paroxysmal tachycardia -peripheral vascular disease	Post operative urine retention -paralytic ileus	-miotic eye drops in glucoma -Post operative urine retention -paralytic ileus

N.B: never given IV or IM

Indirect Parasympathomimetics (Anti-cholinesterases)

inhibet Cholinesterase

	Reversible	Irreversible
Binding to enzyme	loose	Firm
Enzyme activity	Can be regained	Can not
Action duration	short	Long
example	**physostigmine, neostigmine, edrophonium**	➢**organophosphorus compounds** **Ecothiopate(antiglucoma drug)** **Malathion, parathion(antiscabes)** **Metrifonate(antihelminthic)**

Reversible anticholine estrase

	Physostigmine	Neostigmine
	natural	Synthetic
	Tertiary amine	Quaternary amonium
Kinetics		
dynamics	M: mainly on eye N:muscle twitches, no direct action CNS: stimulation	M: GIT, urinary N: muscle twitches+direct stimulation CNS: no
uses	-Glaucoma -Counteract action of mydriatic -Alternative with mydriatic to cut recent adhesion ( ) iris &lens -ttt of alzheimer disease	-Post operative urine retention -paralytic ileus - Myathenia gravis - Antidote to curare toxicity
toxicity	M: bradycardia, hypotension, bronchospasm, miosis, diarrhea, ++secretions N:muscle twitches: eye lid,face CNS: convulsion, collapse,coma	NO CNS manifistions
ttt of toxicity	Stomache wash, anticonvulsant,oxygen, atropine is an antidote	

➢ Nicotin and smoking

- *Mechanism o(action :*
- 1- Stimulate sympathetic ganglia and adrenal medulla,
- 2- Release of catecholamine from nerve end and chromoffin cell.
- *CVS:*The cardiovascular effects of nicotine is due to increase release of adrenaline from suprarenal gland as a result of stimulation of nicotine receptors in suprarenal gland.
- - Tachycardia, increase cardiac output.
- - increasing excitability ------ extrasystole .
- - Angina due to increase heart work without coronary dilatation.
- - Vasocontriction of all blood vesse1es leading to:
- Hypertension due to constriction of systemic arterioles
- Retinal ischemia and scotomata (localized areas of loss of vision due to constriction of retinal arterioles.
- Peripheral ischemia due to peripheral vascular diseases.
- Teratogenicity due to constriction of uterine blood vessels in pregnant women
- - Increase free fatty acids , Platelet stickness -- atherosclerosis, thrombosis .
- **Uses**:Nicotine lozyenges are used in treatment of addiction of cigarette smoking .They maintain long standing minimal concentration of nicotine in plasma that prevent symptoms of nicotine withdrawal.now replaced by **Varneclin**

Irreversible anticholine estrase

Organophosphorus compounds: synthetic compounds have the capacity to bind covalently to acetylcholinesterase.

- The result is a long-lasting increase in acetylcholine at all sites where it is released. Many of these drugs are extremely toxic

Manifestation of toxicity

- Bradycardia and hypotension
- Constricted pupill (miosis)
- Tightness of the chest with dyspnea.
- Nausea, vomiting, abdominal colic and diarrhea.
- Increase of salivation and sweating.
- Muscle twitches
- convulsions.

- **Management Of organophosphate poisoning:**

- 1- Endotrachial intubation with artificial respiration.
- 2- Atropine 2 mg I.V. repeated until signs of atropinization appears. (Dry mouth , dilated pupill , tachycardia) .
- 3- Barbiturates to check convulsions.
- 4- Fresh blood transfusion.

Block the muscarinic

Because the new blood has source for new enzyme

- 5-Oximes (PAM, pralidoxime). at the first 12 h
- The treatment with Oximes should be within hours (2gm in 5% Dextrose I. V. drip).
- Oximes produce their effect through:-

a) Direct reaction with inhibited enzyme.

b) Reactivation of inhibited enzyme.

Separation the enzyme from Receptor

Parasympatholytic Drugs

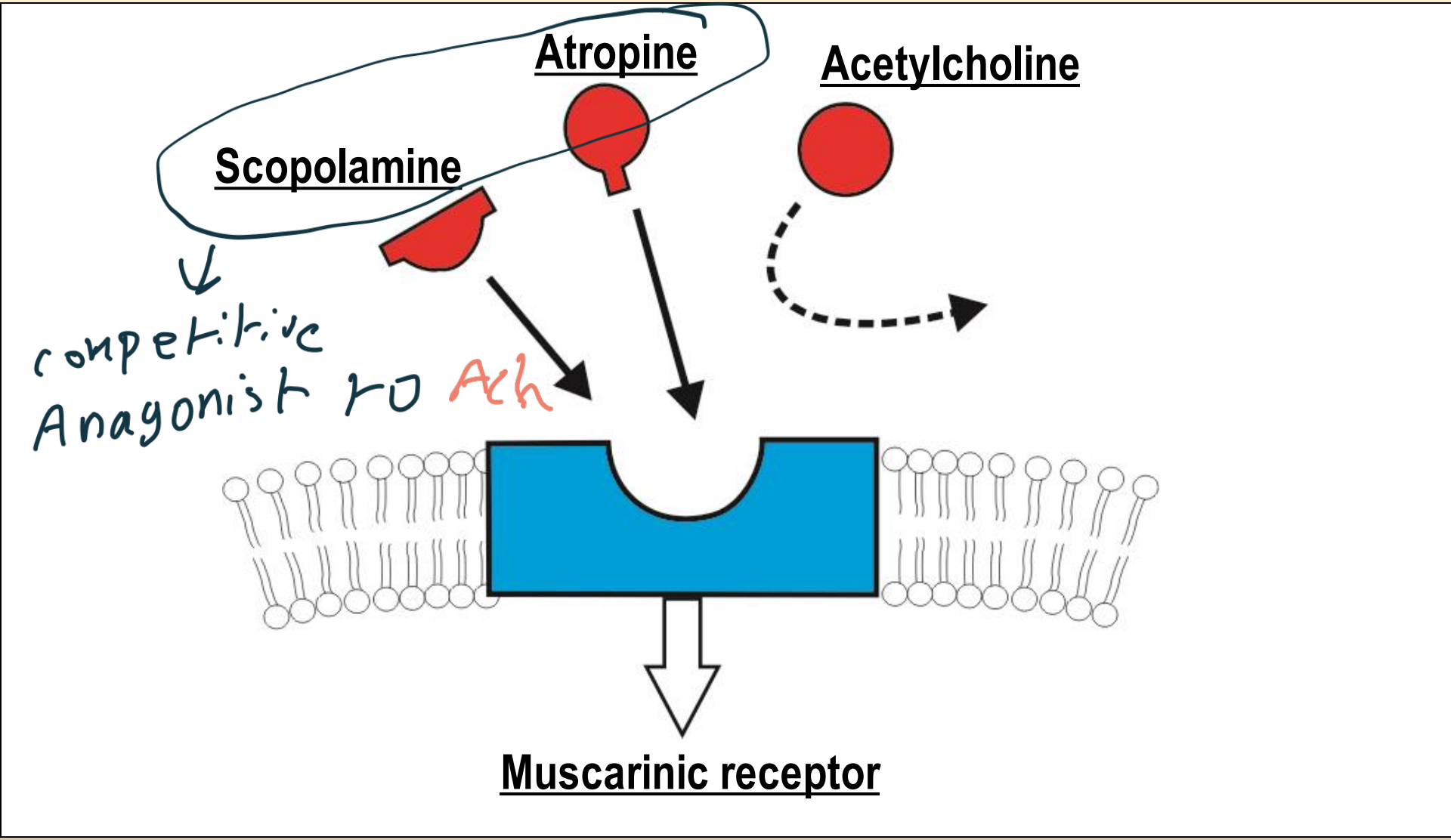
PARASYMPATHOLYTICS (ANTICHOLINERGICS):

Drugs that reduce or inhibit some or all of the actions of the parasympathetic nervous system.

- Muscarinic receptor antagonists
- Nicotinic receptor antagonists
  - Ganglionic blocking drugs (Nn) — not specific
  - Neuromuscular blocking drugs (Nm) — specific

Competition of atropine and scopolamine with acetylcholine for the muscarinic receptor.

Atropine is a competive revesible antagonist at all types of muscarinic receptors

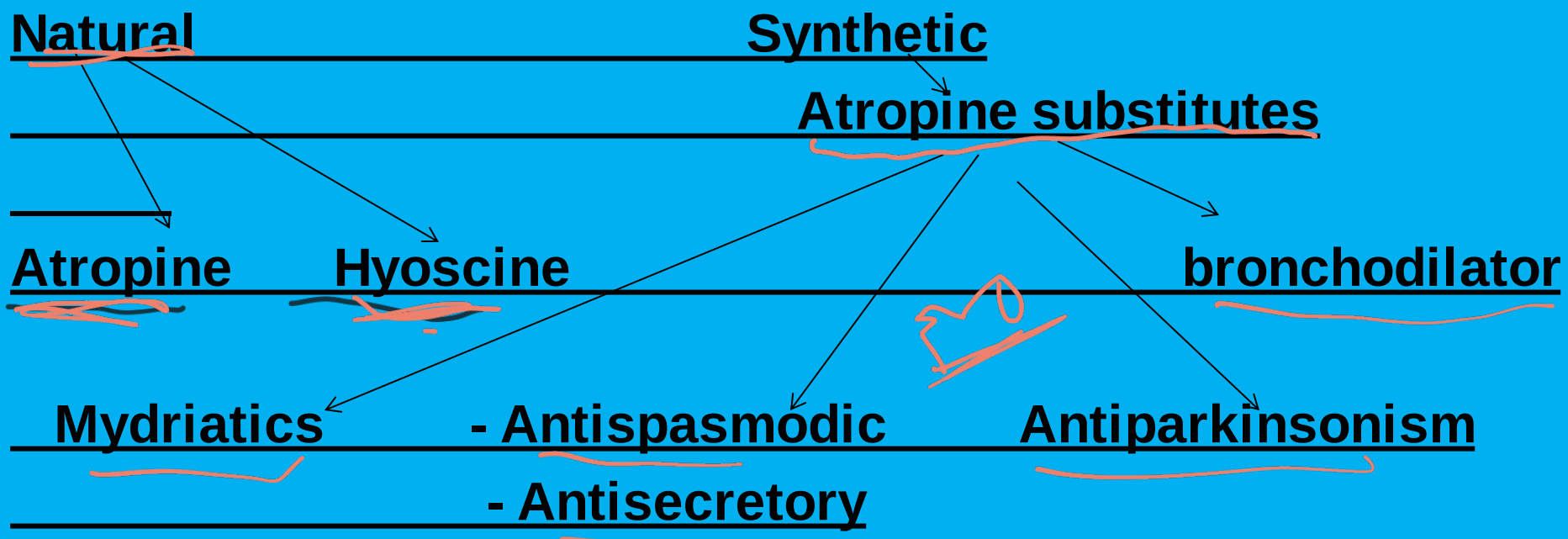


/1/ ANTIMUSCARINIC AGENTS

Block M receptors ⇒ inhibition of all parasympathetic functions.

In addition, block the few exceptional sympathetic neurons that are cholinergic (sweat glands).

Because they do not block N receptors ⇒ the antimuscarinic drugs have little or no action at neuromuscular junctions or autonomic ganglia.



1- Atropine

- **Source and chemistry**
- **Pharmacokinetics**
- **Absorption**
- **Distribution**
- **Metabolism**
- **execretion**

- **Pharmacodynamics**

- **Mechanism of action :Competitive antagonist to A.ch. at Ml ,M2,M3 receptors.**

Parasympatholytic effect on:

I-CVS:

1-Heart

2- blood vessels

3- blood pressure

- It revers hypotensive effect of Ach, carbacol and neostigmine(M, N) action

- It abolish hypotensive effect of Methacholine ,Bethanecol and Pilocarbine(M)action only

II-S.M.F:

1- Eye

2- bronchi

3- GIT

4- Urinary

III-Secretions: it decrease all body secretions except (milk ,bile and urine)

I-CVS:

1-Heart: with low dose: initial bradycardia?? Then with larger dose the cardiac M2 receptor is blocked, and the cardiac rate increases.

2- Circulation: Therapeutic dose ---No-effect due to lack parasympathetic innervation to vascular beds blood vessels

II-S.M.F:

- Eye: passive mydriasis, cycloplegia (inability to focus for near vision), increase of IOP and Loss of light reflex & Decrease lacrimation

- Bronchioles:

Bronchodilatation & decrease bronchial secretion.

- GIT: Used as an antispasmodic to reduce activity of the GIT. Although gastric motility is reduced, HCl production is not reduced »»» not very effective in healing of a peptic ulcer. Pirenzepine, an M1-muscarinic antagonist, is effective in reducing gastric acid secretion.

- Urinary system: Reduces hypermotility states of the urinary bladder. Occasionally in enuresis in children. **Emepronium** is better than atropine.

III-Secretions: Inhibition of secretions (salivary, lacrimal, bronchial and sweat gland inhibited »»»» drying effect on membrane (xerostomia)

Actions on CNS: stimulant and depressants ,but mainly stimulant 3/2

-Stimulation of

*Therapeutic dose stimulate C.I.C leading to initial bradycardia. If it is given I.V

*Large doses stimulate R.C leading to tachypnea

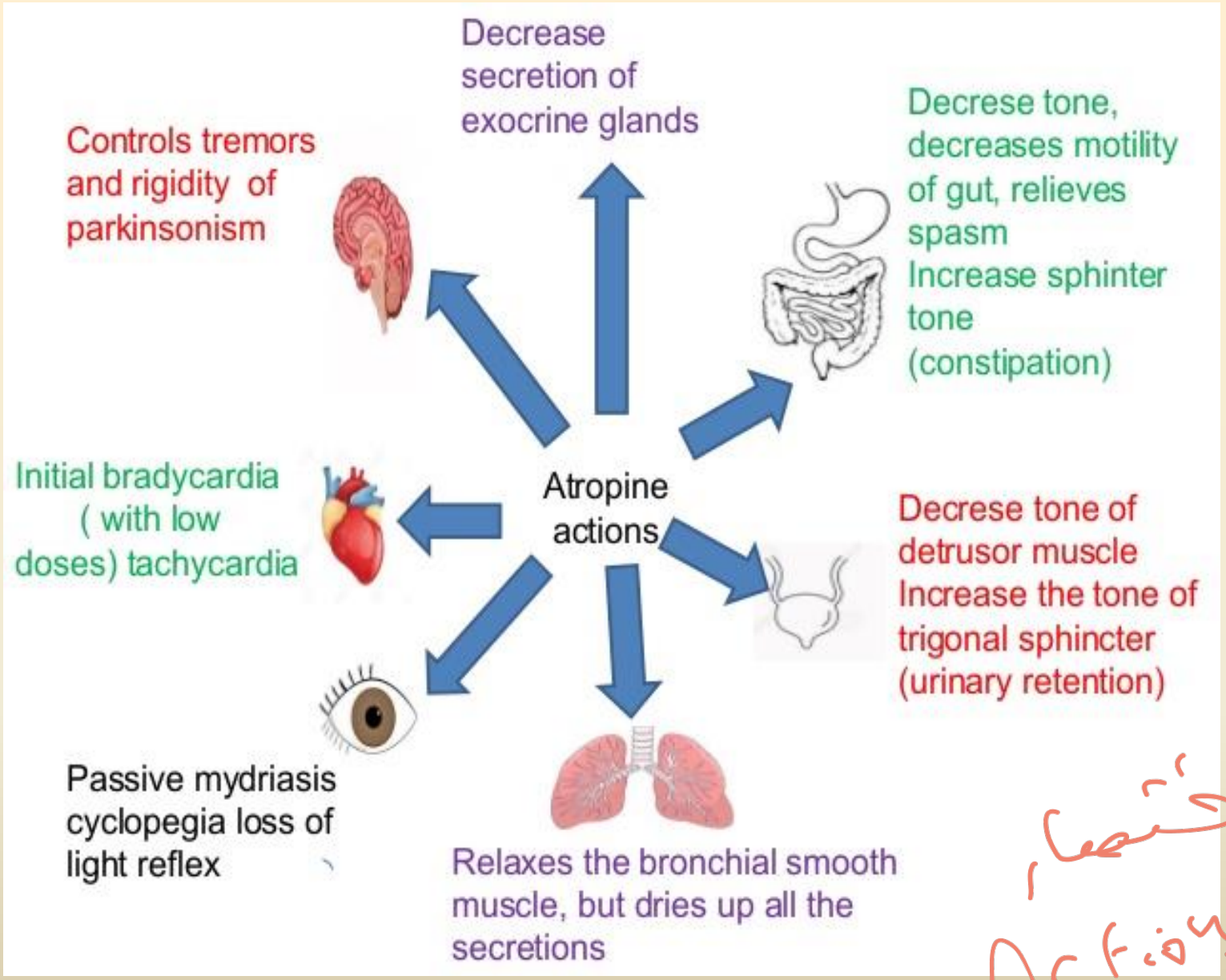
*Toxic doses causes restlessness , hallucination, delirium followed by depression and coma.

-Depression of :

*Muscle tone (antiparkinsonian effect =treatment of rigidity and tremors in parkinsonism).

*Vomiting center (antiemetic effect).

- It has local anesthetic action



اختصار Action of Atropan

Therapeutic uses

Therapeutic Uses:

1- Preanesthetic medication:

A -counteract excess vagal tone during operation

B- decrease salivary secreations (prevent bronchopneumonia) and decrease bronchial secreations (prevent lung collaps)

2- treatment of physiostigmine and organophosphorous toxicity

3-Parasymatholytic (systems)

1-CVS :heart block (due to infarction and digitalis toxicity) and sever bradycardia

2-Eye: fundus examination (derivatives is better) due to long duration of action

3-Respiration:bronchial asthma while (ipratropium is better)

4-GIT: intestinal colic ,antiemetic, antidiarrheal and peptic ulcer

5- urinary : renal colic and nocturnal enuresis(Emepronium is better derivative)

6- secretions :hyperhidrosis(excess sweating)

7- CNS: antiparkinsonial

Side effects:

1- Dryness of mouth, blurred vision, sinus tachycardia.

2- Retention of urine especially in old patients with enlarged prostate

3- Acute glaucoma: old patients are more susceptible

4- Increase temperature in children.

Contraindication:

1- Tachycardia or arrhythmia

2- Glaucoma

3- Constipation or paralytic ileus → problem in intestin

4- Senile enlargement of prostate

**Acute atropine poisoning:

1- Parasympathetic depressant symptoms: Dry mouth, tachycardia, mydriasis, loss of accommodation, decrease sweating (fever).

2- Skin ----- hot, dry, flushed (compensatory superficial cutaneous vasodilation to increase heat loss).

3. C.N.S. restless, excitement, hallucinations, mania, delirium, depression, death.

-Treatment of acute atropine poisoning:

Gastric lavage orally. Artificial respiration. Ice bags. Alcohol spinges--decrease fever. Parasympathomimetics. (neostigmine is specific anti dote) & Sedatives.

2- Hyoscine (scopolamine)

	Atropine	hyoscine
Duration of action	Long duration 7-10 days	Short duration 4-7 hours
Action :1-dominant PS action	CVS , GIT, Urinary	Eye and secretions
2- CNS	Both stimulant and depressant but mainly stimulant	Both stimulant and depressant but mainly depressant -sedation, hypnosis and -amnesia to recent events - Antimotion sickness -Antiparkinsonial
		Stimulant effect ++RC Excitation and hallucination with over dose
Local anesthetic action	Present	absent

Therapeutic uses:

1- Preanaesthetic medication preferred to atropine: because it produces more CNS depression .It is potent amnesic , stronger antisecretory and antiemetic .

2- Antispasmodic.

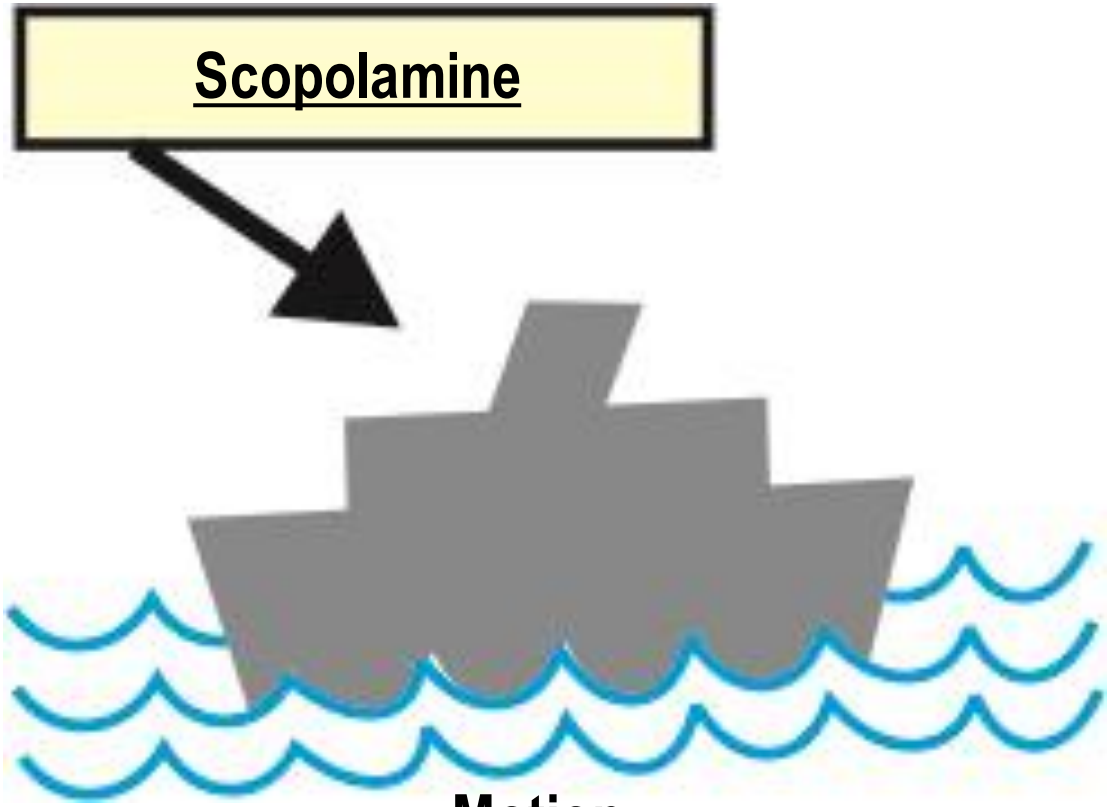
3- Prophylaxis of motion sickness.

4- Sedative in mania.

7 - Antiparkinsonian agent

and Antimotion sickness

Scopolamine is an effective anti-motion sickness agent.



For nausea due to ……

Motion Sickness

Main clinical uses of muscarinic antagonists

Cardiovascular

- Treatment of sinus bradycardia (e.g. after MI: atropine).

Ophthalmic

- To dilate the pupil: e.g. tropicamide eye drops or cyclopentolate eye drops (longer acting).

Neurological

- Prevention of motion sickness: e.g. hyoscine (orally or transdermally).
- Parkinsonism, especially to counteract movement disorders caused by antipsychotic drugs: e.g. benztropine.

dilatation and decrease secretion

Respiratory

- Asthma: **ipratopium by inhalation.**

Anaesthetic premedication

- To dry secretions: e.g. atropine. hyoscine (however, current anaesthetics are relatively non-irritant - less important.)

GIT

- To facilitate endoscopy and gastrointestinal radiology by relaxing gastrointestinal smooth muscle (antispasmodic action), e.g. hyoscine.
- As an antispasmodic in irritable bowel syndrome or colonic diverticular disease
- To treat peptic ulcer disease by suppressing gastric acid secretion, e.g. pirenzepine (M_1- selective antagonist). Now less used - introduction of histamine H_2-antagonists and proton pump inhibitors.

THANK YOU