INDIRECT CHOLINOMIMETICS

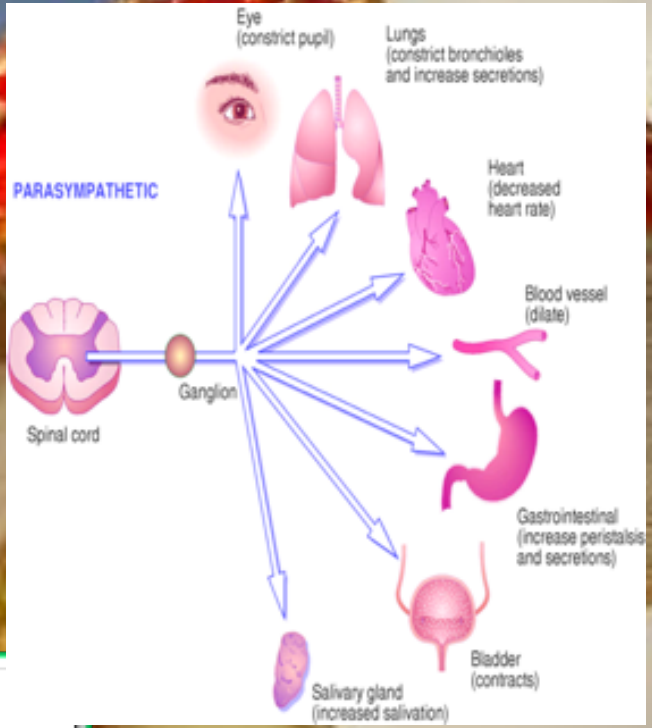
ILOS

To identify the mechanism of action of indirect acting acetylcholine receptor stimulants

To discuss the pharmacokinetic aspects and pharmacodynamic effects of indirect cholinomimetics

To outline the therapeutic uses and toxicity of indirect cholinergic agonists

To highlight the therapy of cholinergic toxicity



INDIRECTLY –ACTING CHOLINOCEPTOR STIMULANTS:-

1. quaternary ammonium groups

edrophonium

quaternary amine

neostigmine

tertiary amine

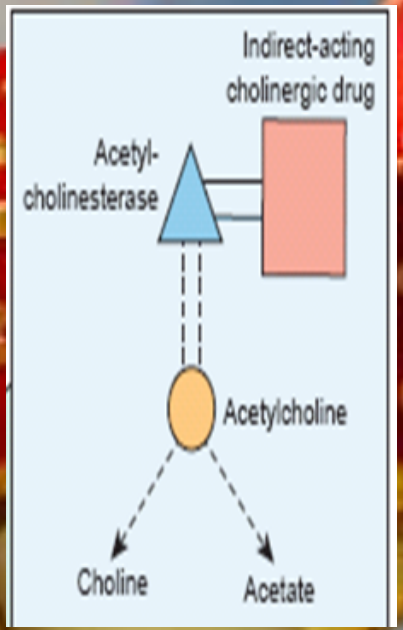
physostigmine

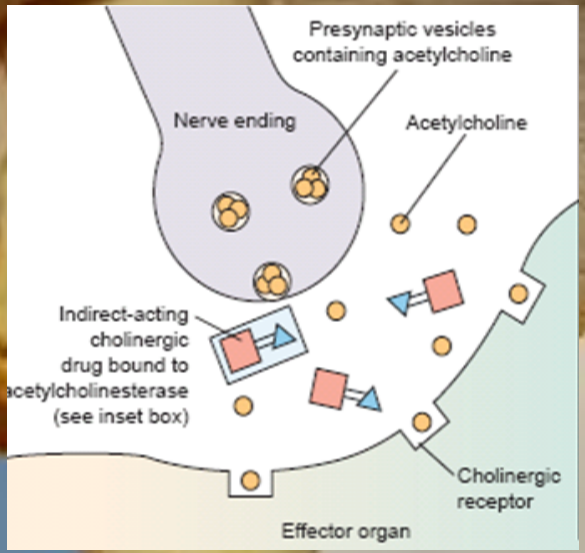
3-Organophosphates

Most of the organophosphates are highly lipid soluble except **ecothiopate**

MECHANISM OF ACTION

↓Aetylcholinesterase→↑level of endogenous Ach.





MECHANISM OF ACTION

Edrophonium

Bind reversibly by electrostatic forces to the active site, preventing access of Ach , enzyme-inhibitor complex is short lived'2-10min'

Carbamate esters

Physostigmine(non-polar), neostigmine, pyridostigmine

Form covalent bond, more resistant to hydrolysis' 0.5-6hr'

MECHANISM OF ACTION

Organophosphates

Phosphorylate enzyme ,hydrolysis very slow **'hundreds of hours'**.

Due to the long duration they are called **irreversible inhibitors**

Pralidoxime is used as cholinesterase **regenerator** for organic phosphate poisoning

PHARMACOKINETICS

Absorption of quaternary ammonium salts is poor (ionized)

Distribution in the CNS is negligible

Physostigmine well absorbed can be used topically in the eye

Carbamates are relatively stable in aqueous solution, but can be metabolized by esterases

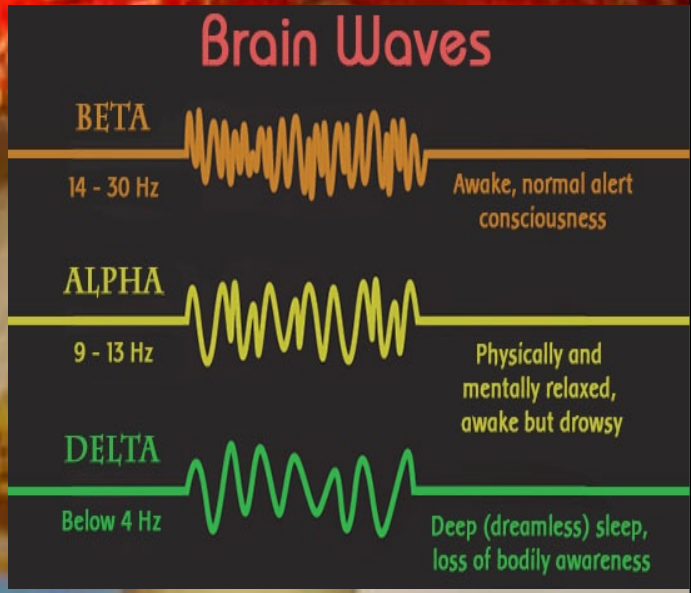
Organophosphates , well absorbed from the skin , lung, gut & conjunctiva except ecothiopate, (less stable in aqueous solution)

PHARMACODYNAMIC EFFECTS

Primary effect is to potentiate the action of **endogenous Ach**

1-CNS

In low concentration:- The high lipid-soluble inhibitors cause diffuse activation of **EEG**→ alerting response(ß wave)



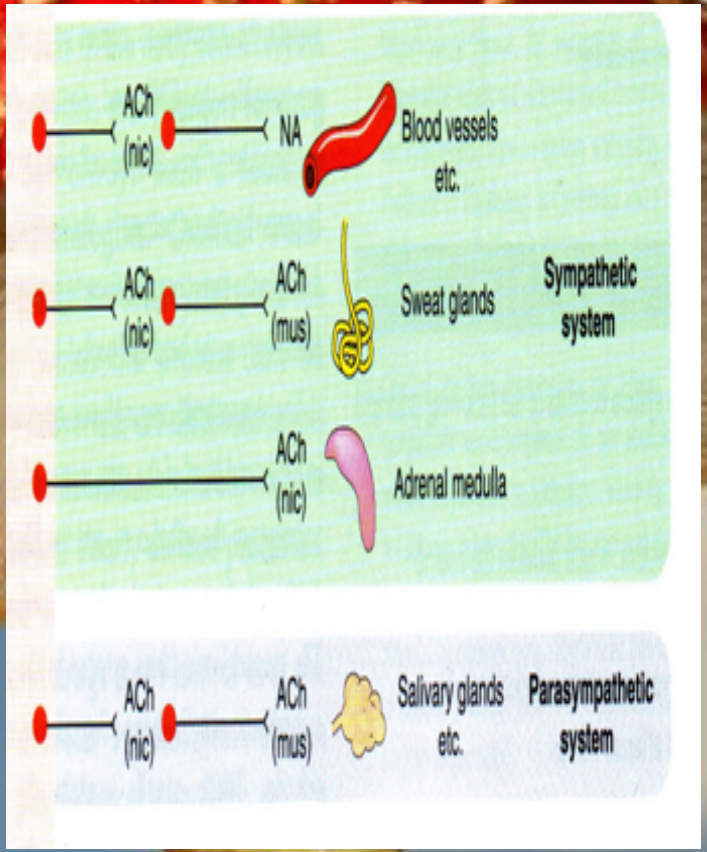
↑Concentration →generalized convulsions followed by **coma** & respiratory arrest

PHARMACODYNAMIC EFFECTS

2-CVS

Activation in both sympathetic & parassympathetic ganglia & neuroeffector junction

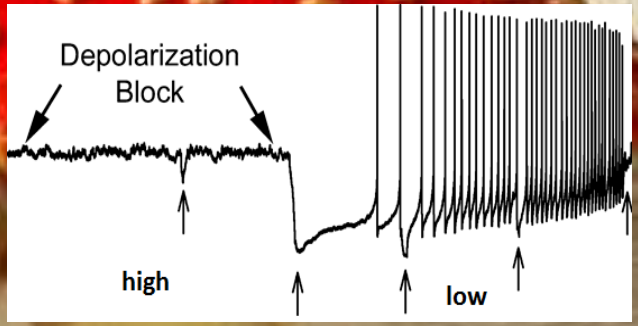
In the heart effects of **parasympathetic** limb predominate, ↓HR, ↓conduction velocity through AV node, ↓atrial contractility, ↓CO. Modest change in Bp.



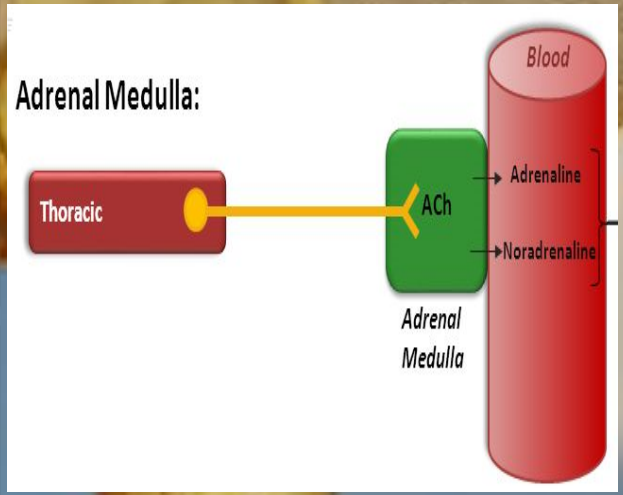
PHARMACODYNAMIC EFFECTS

3-Neuromuscular junction

Low concentration → Intensify the effect of endogenous Ach
↑ force of contraction



High concentration →fibrillation of muscle fibers, membrane depolarization becomes sustained → depolarization block



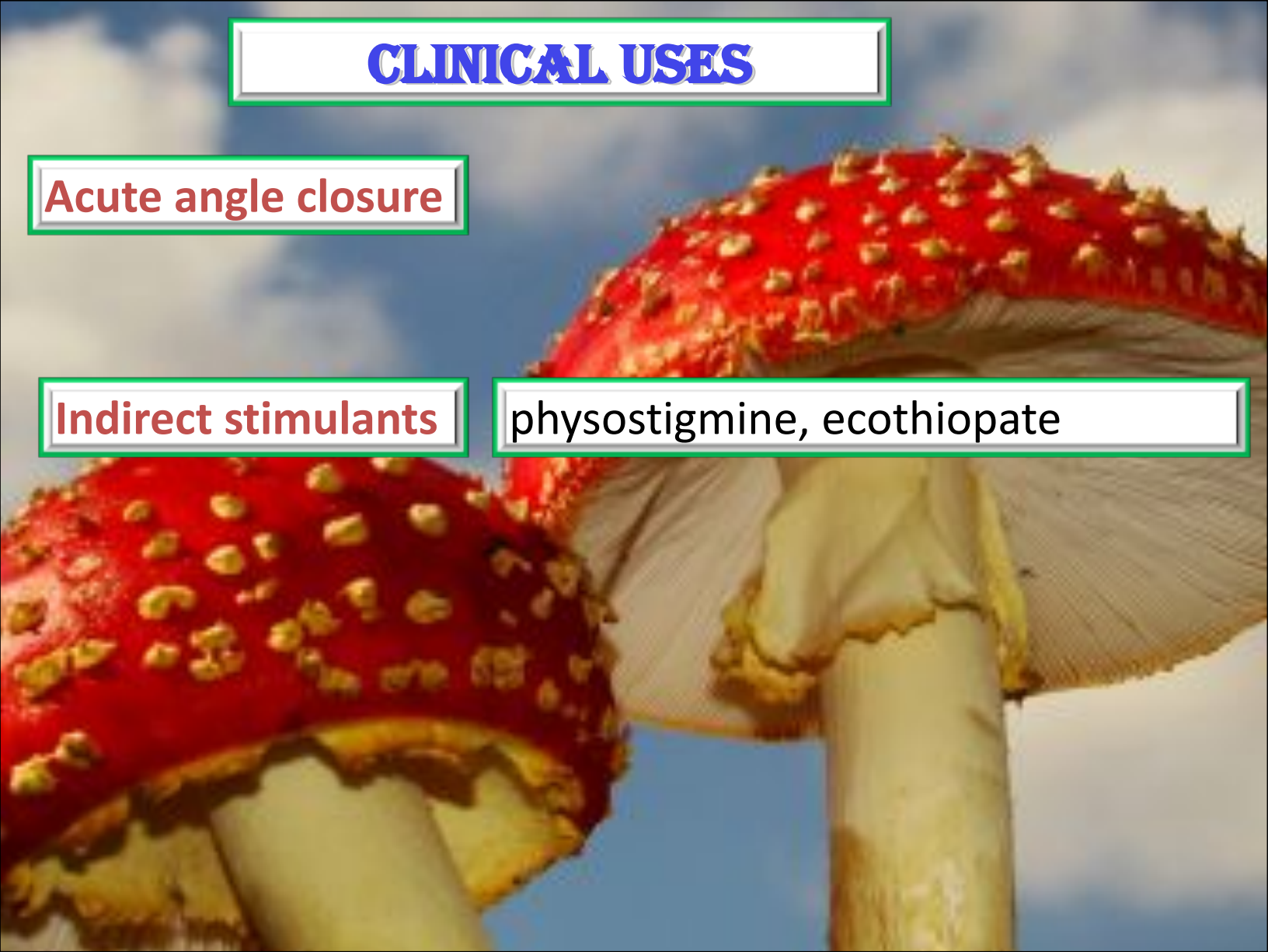
Adrenal medulla

Release of catecholamines

CLINICAL USES

Acute angle closure

Indirect stimulants — physostigmine, ecothiopate



CLINICAL USES

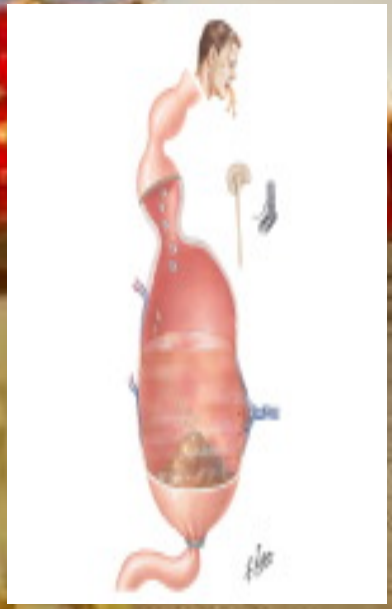
2-GIT & Urinary tract

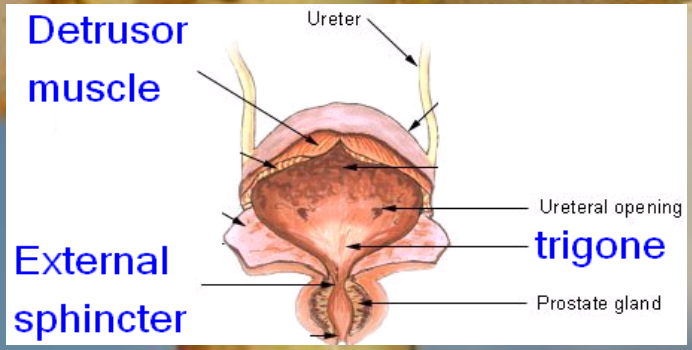
Postoperative ileus "**atony** or paralysis of the stomach following surgery

Postoperative **urinary retention**

Neostigmine

Xerostomia ⟶ Pilocarpine





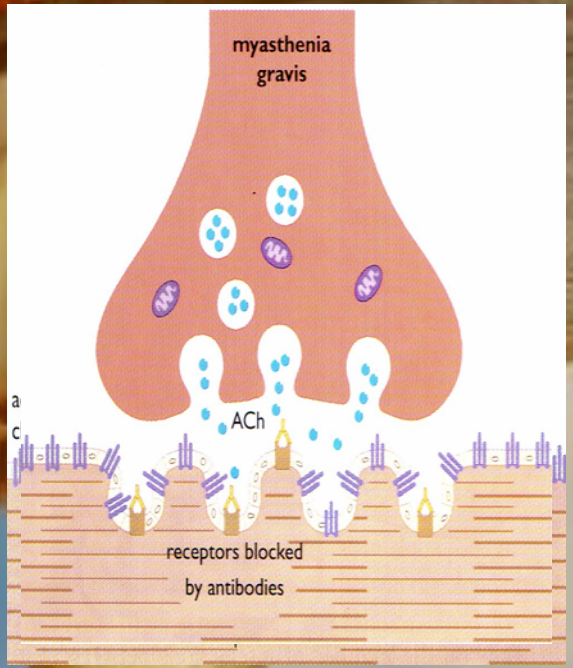
CLINICAL USES

3-Neuromuscular junction:-

Myasthenia gravis

Autoimmune disease

Production of antibodies→ ↓no. of functioning nicotinic receptors at endplate



CLINICAL USES

Myasthenia gravis

→Weakness ,fatigue affecting muscles of hand ,head, neck , extremities

→Ptosis, diplopia, difficulty of speaking & swallowing.

- Treatment with **cholinesterase inhibitors+ immunosupressants**

Myasthenia gravis

Edrophonium is used as(1) **test for diagnosis** . An improvement in muscle strength last for 5min is noted. It is also used(2) to **assess the adequacy** of treatment with the longer –acting cholinesterase inhibitors

- In case of excessive amount of cholinesterase inhibitor, a patient becomes weak because of **depolarization block** + symtoms of muscarinic stimulation.

If a patient improves with a dose of edrophonium, **an increase in cholinesterase inhibitor is indicated**

Myasthenia gravis

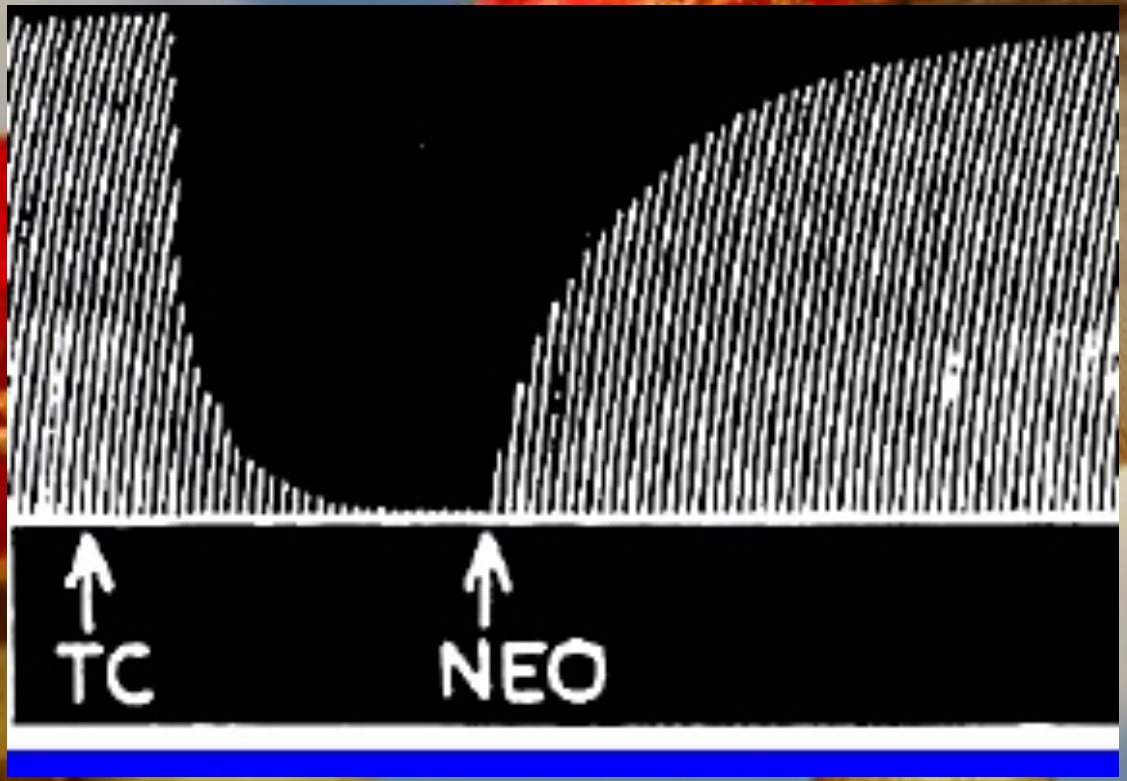
- Severe myasthenia **[myasthenia crisis]**, requires mechanical ventilation

- Excess drug therapy **[cholinergic crisis]**

- Chronic long term therapy→ **neostigmine, pyridostigmine, ambenonium.** Muscarinic side effects can be controlled by antimuscarinics

CLINICAL USES

- **4-To reverse pharmacological paralysis** produced in case of **anaesthetic adjunct (neostigmine versus D-Tubacurarine)**.



CLINICAL USES

5-Heart:- for treatment of supraventricular tachycardia, **edrophonium** potentates the effect of Ach at AV node →slow AV conduction & ventricular rate.

6-Antimuscarinic drug intoxication:- atropine overdose is toxic in children → severe muscarinic block

Blockade is competitive , overdose can be overcome by ↑ amount of endogenous Ach.

Physostigmine is used because it crosses the BBB , reverses central & peripheral signs.

CLINICAL USES

Alzheimer's Disease

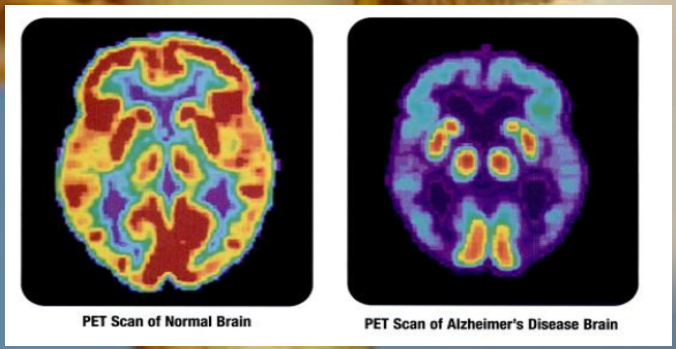
Characterized by loss of cholinergic neurons in the basal forebrain nuclei.

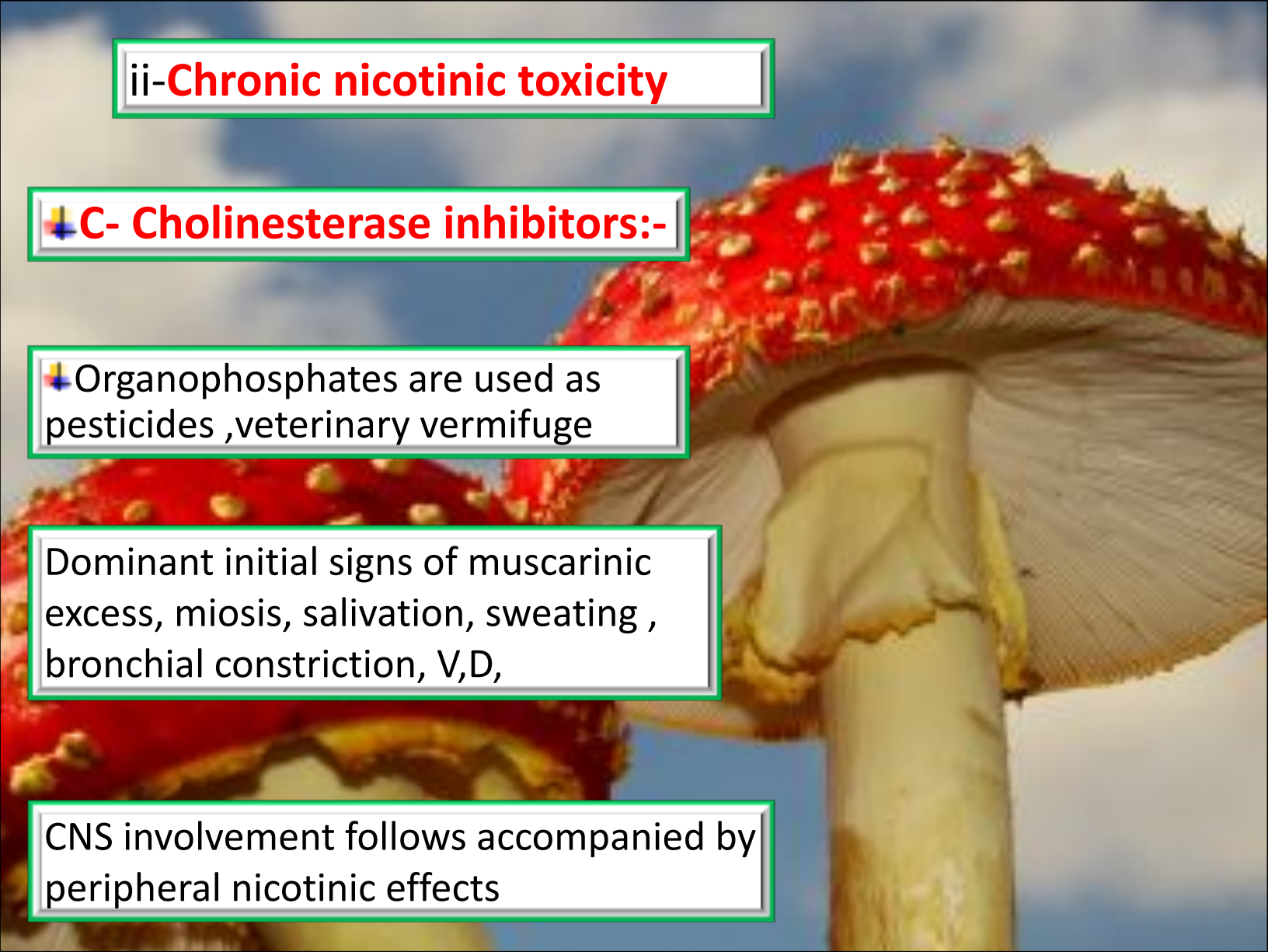
Thus cholinesterase inhibitors are used to treat AD

Donepezil, is not hepatotoxic

Used for treatment of dementia of AD

Taken orally





ii-Chronic nicotinic toxicity

C- Cholinesterase inhibitors:-

- Organophosphates are used as pesticides ,veterinary vermifuge

Dominant initial signs of muscarinic excess, miosis, salivation, sweating , bronchial constriction, V,D,

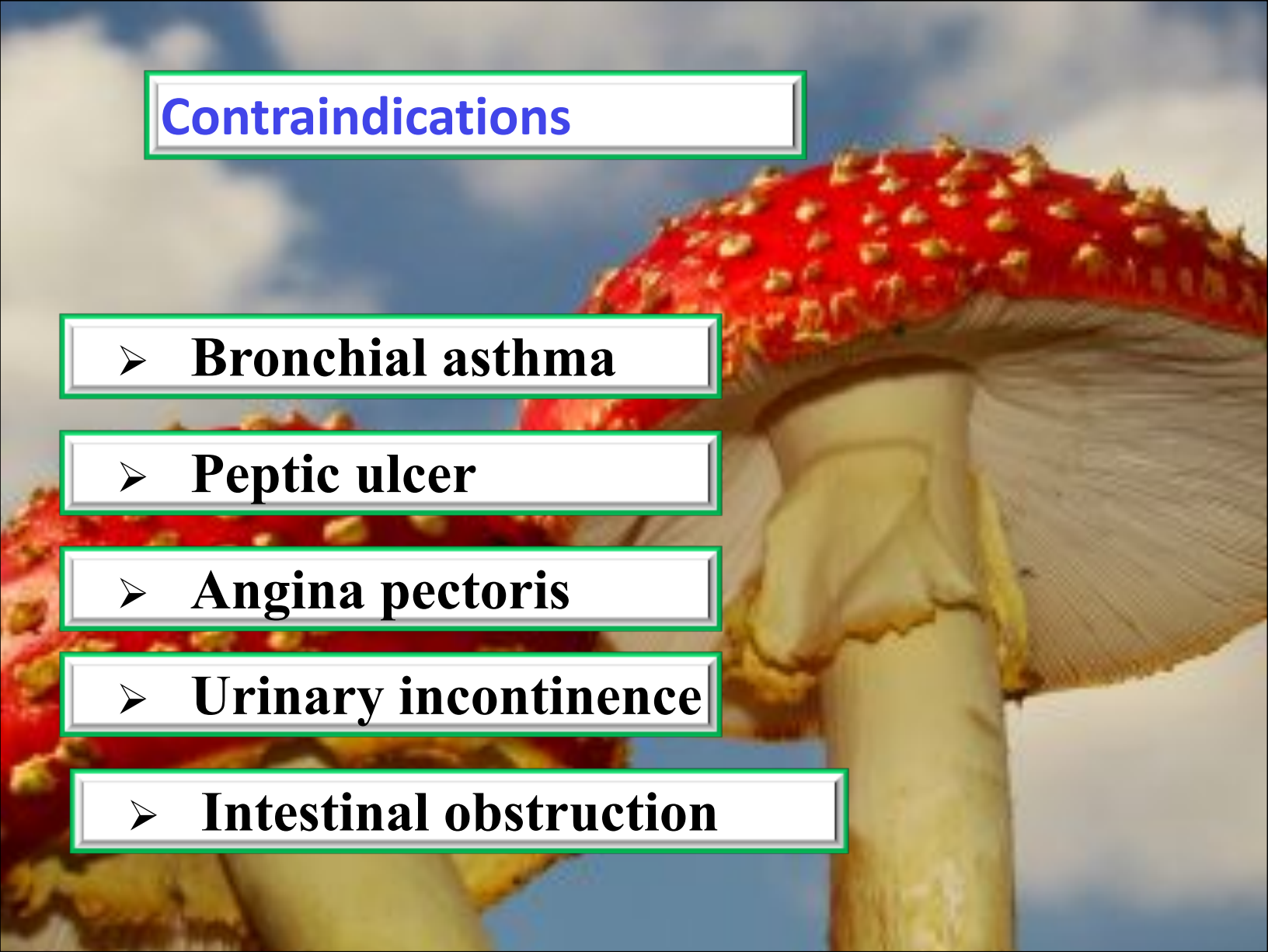
CNS involvement follows accompanied by peripheral nicotinic effects

Therapy of cholinesterse toxicity

1- **Maintenance of vital signs** , respiration may be impaired

2-**Decontamination** to prevent further absorption, removal of cloth, washing of skin

Parenteral atropine in large doses.
Pralidoxime[PAM][oxime] often



Contraindications

- Bronchial asthma
- Peptic ulcer
- Angina pectoris
- Urinary incontinence
- Intestinal obstruction

Muscarinic actions

Organs	Cholinergic actions
Eye	Contraction of circular muscle of iris (miosis)(M3) Contraction of ciliary muscles for near vision (M3) Decrease in intraocular pressure
Heart endothelium	bradycardia (↓ heart rate) (M2) Release of NO (EDRF)
Lung	Constriction of bronchial smooth muscles Increase bronchial secretion M3
GIT	Increased motility (peristalsis) Increased secretion Relaxation of sphincter M3
Urinary bladder	Contraction of muscles Relaxation of sphincter M3
Exocrine glands	Increase of sweat, saliva, lacrimal, bronchial, intestinal secretions M3

Carbamate esters

Drug	Actions	Kinetics	Uses
Neostigmine	Nicotinic & muscarinic M, N	0.5-6 hr polar	Myasthenia gravis treatment Paralytic ileus Urinary retention Curare toxicity
Physostigmine	Nicotinic muscarinic M, N, CNS	0.5-2hr Lipid soluble	Glaucoma atropine toxicity
Pyridostigmine	Nicotinic & muscarinic M, N	3-6 polar	Myasthenia gravis treatment
Ambenonium	Nicotinic & muscarinic M, N	4-8 polar	Myasthenia gravis treatment

Indirect Cholinomimetic

Edrophonium M, N	Very Short 5-15 min, Polar	Diagnosis of Myasthenia gravis
Neostigmine M, N	Short 0.5-2hr polar	Myasthenia gravis treatment Paralytic ileus Urinary retention curare toxicity
Physostigmine M,N, CNS	Short 0.5-2hr Lipid soluble	Glaucoma atropine toxicity
Ambenonium Pyridostigmine M, N	Short 3-6, polar	Myasthenia gravis treatment
Ecothiophate M, N	Long 100hr, polar	Glaucoma.
Donepezil M, N		dementia of Alzheimer's disease