Cholinergic system part 2

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Cholinesterase inhibitors (Anticholinesterases)

Are drugs that prevent degradation of Ach by cholinesterase, are of 2 types:

1.Reversible- produce effects of moderate duration

2.Irreversible- produce long lasting effects

Reversible cholinesterase inhibitors (anticholineterase)

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

*Is a synthetic reversible anticholinesterse

*action is more prominent on NM junction & alimentary tract than CNS, CVS & eye.

*It contains quaternary nitrogen atom

*so it cannot readily cross membranes including of GIT, BBB & placenta,

*so it is poorly absorbed after oral administration.

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.

Therapeutic uses

1.myasthenia gravis

2.reversal of non-depolarizing NM blockade

2)Physostigmine

is similar to neostigmine, but is

- **not quaternary ammonium compound**
- **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

3)Pyridostigmine

is similar to neostigmine, but it has

- **slower onset of action**
- **slightly longer in duration**
- **fewer visceral effects.**

Is used in myasthenia gravis

4)Edrophonium

is structurally related to neostigmine but

its action is brief

autonomic effects are minimal except in high doses.

Uses

1.diagnosis of myasthenia gravis

2.to differentiate between myasthenic crisis(is improved) and cholinergic crisis (is aggravated)

Adverse effects of cholinomimetic drugs

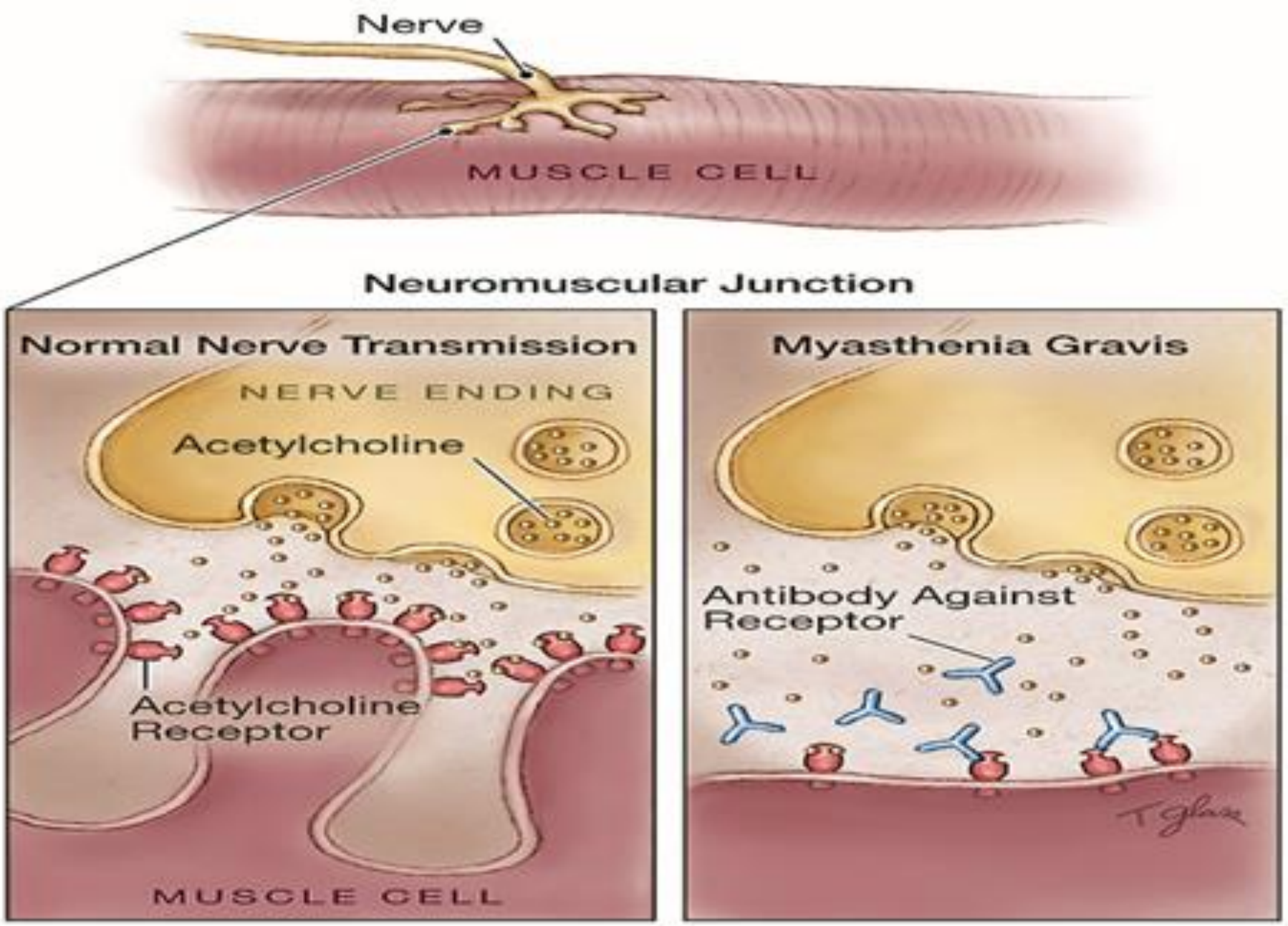
- **Miosis, Lacrimation**
- **Excessive salivation**
- **Increased gastric secretions, increased tone & motility of GIT—colicky abdominal pain, diarrhea**
- **Bradycardia, hypotension**
- **Bronchospasm, bronchorrhea**
- **Urinary urgency**
- **Sweating**

Precautions & contraindications to cholinomimetic drugs

1. Mechanical obstruction of GIT & urinary tract
2. peptic ulcer
3. bronchial asthma
4. coronary insufficiency and bradycardia

Myasthenia gravis

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


Nerve
MUSCLE CELL
Neuromuscular Junction
Normal Nerve Transmission
NERVE ENDING
Acetylcholine
Acetylcholine Receptor
MUSCLE CELL
Myasthenia Gravis
Antibody Against Receptor

Clinical features

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

Ptosis (drooping of the eyelid)

Diagnosis

1. Edrophonium i.v, it will dramatically & transiently relieve myasthenic muscular weakness.

2.measurement of Ach receptor Abs titer to confirm diagnosis

Treatment

1.symptomatic- Anticholinesterase

pyridostigmine is preferred because its action is smoother than neostigmine.

Neostigmine has more rapid onset of action so has 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.**

Irreversible cholinesterase inhibitors

***Are highly toxic, used 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 active center of cholinesterase so preventing the enzyme from hydrolyzing Ach.**

***Because of irreversible binding, effects persist until new molecules of cholinesterase can be synthesized.**

Typical features of acute poisoning

1. **CNS- anxiety, headache, convulsions, respiratory failure**
2. **Eye- miosis, excessive lacrimation**
3. **GIT-salivation, vomiting, abdominal cramps, diarrhea, involuntary defecation**
4. **Respiratory system-bronchoconstriction, increased bronchial secretions, cough, wheezing & dyspnea**

5.CVS-bradycardia, hypotension

6.GUT-involuntary micturition

7.Skin- excessive sweating

8.Skeletal system- muscle twitching and weakness

- **Death is due to respiratory failure caused by:**

a-action in CNS causing respiratory center depression

b- respiratory muscles paralysis

c- excessive bronchial secretions & bronco-constriction

- S Salivation, sweating
- L Lacrimation
- U Urination
- D Defecation
- G Gastrointestinal cramps
- E Emesis

SLUDGE , MBC

- M Miosis, Muscle Weakness
- B Bradycardia, Bronchospasm, Bronchial Hypersecretion
- C Convulsion, Coma, Central respiratory depression

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 active center of cholinesterase.

It is given by a slow i.v injection over 5-10 min.

Limitations of pralidoxime:

1. **Its efficacy is decreased if administered after 12 hours of poisoning**
2. **It can not cross BBB, so can not reverse cholinesterase inhibition in CNS.**

The only therapeutic use of irreversible anti cholinesterases is in glaucoma & one drug is available (echothiopate).

Questions

- **The following are features of organophosphorous poisoning except**
- **A. tachycardia**
- **B. involuntary urination**
- **C. excessive sweating**
- **D. abdominal cramps**
- **E. respiratory failure**


Thank You