Peripheral Nervous System (PNS)

Pharmacology (2)

Indirectly acting cholinergic agonists

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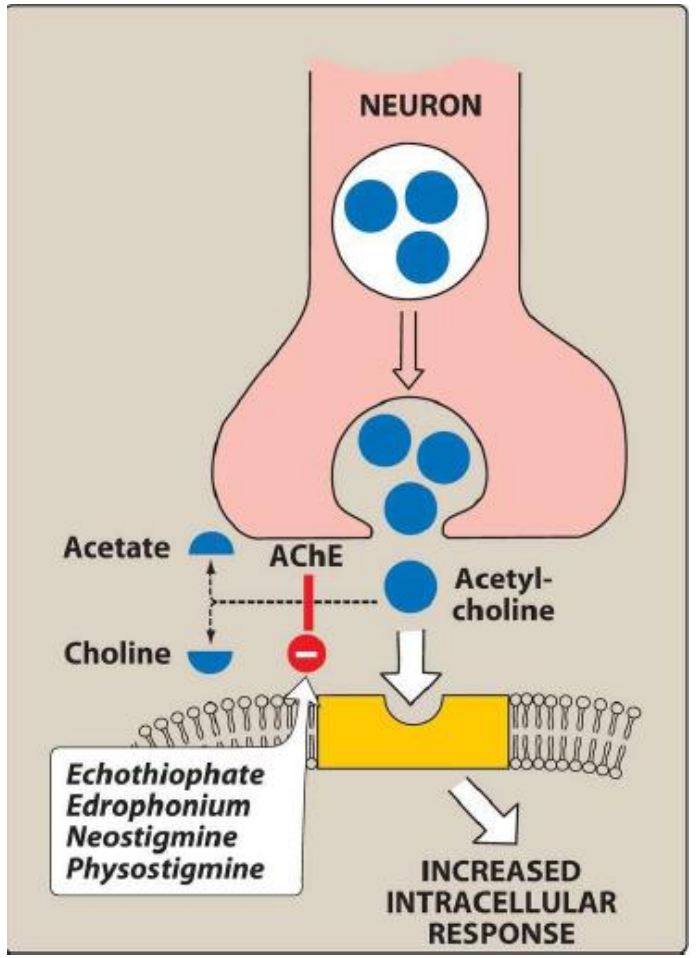
Indirectly acting cholinergic agonists

- Anticholinesterase agents or cholinesterase inhibitors indirectly provide cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space.
- Provoke a response at all cholinoceptors, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain.
- Divided into reversible and irreversible inhibitors.



Edrophonium

Reversible inhibitor of AchE*, with* short DoA (10-20 mins) due to rapid renal elimination. Contains a quaternary amine, and its actions are limited to the periphery (does not cross the blood-brain barrier).

- **Therapeutic uses**:

1. Diagnosis of myasthenia gravis (Tensilon test): an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes the degradation of the nicotinic receptors, making fewer receptors available for interaction with ACh. Intravenous injection of *edrophonium* leads to a rapid increase in muscle strength in patients with myasthenia gravis.
2. Reversing the effects of nondepolarizing neuromuscular blockers (Competitive ACh antagonists) after surgery: neostigmine is preferred due its longer duration of action and higher potency.
3. Differential Diagnosis of Myasthenia Gravis vs. Cholinergic Crisis: I.V edrophonium, produces clinical improvement in myasthenic crisis but worsening of symptoms in cholinergic crisis. Myasthenia crisis medical emergency due rapidly progressive weakness of the respiratory muscles.

- Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote).

Physostigmine

- *Physostigmine* is a natural alkaloid found in plants (calabar beans).
- Reversible inhibitor has fast onset (5-10 min), intermediate acting drug (DoA: 30 min to 2h depends on severity of anticholinergic toxicity).
- Muscarinic stimulation can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension. Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). ***Physostigmine* can penetrate the CNS.**

➢ **Therapeutic uses**

1. Anticholinergic overdose: antidote for poisoning with anticholinergics. Used to reverse toxic, life-threatening delirium caused by an anticholinergic agent (atropine, scopolamine, diphenhydramine). Symptoms associated with anticholinergic toxicity are delirium, tachycardia, mydriasis, urinary retention, dry skin.
2. Delayed Emergence from Anaesthesia

➢ **Adverse effects**

High doses of *physostigmine* may lead to convulsions. Bradycardia and a fall in cardiac output may also occur. Continuous depolarization, results in paralysis of skeletal muscle.

Neostigmine

Neostigmine a synthetic compound with quaternary nitrogen. Absorbed poorly from the GI tract, and **does not enter the CNS.**

- **Actions**

Its effect on skeletal muscle is greater than physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has an intermediate duration of action, usually 30-2 hours.

- **Therapeutic uses:**

1. Postoperative urinary retention: for both prevention and treatment of urinary distention and retention,
2. Reversal of nondepolarizing neuromuscular blockade after surgery.
3. Symptoms management of myasthenia gravis: pyridostigmine is more commonly used.
4. Neurotoxic snakebite when antivenom is not available or is ineffective.

- **Adverse effects**

include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. **Not used** to overcome toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is **contraindicated** when intestinal or urinary bladder obstruction is present.

Tacrine, donepezil, rivastigmine, and galantamine

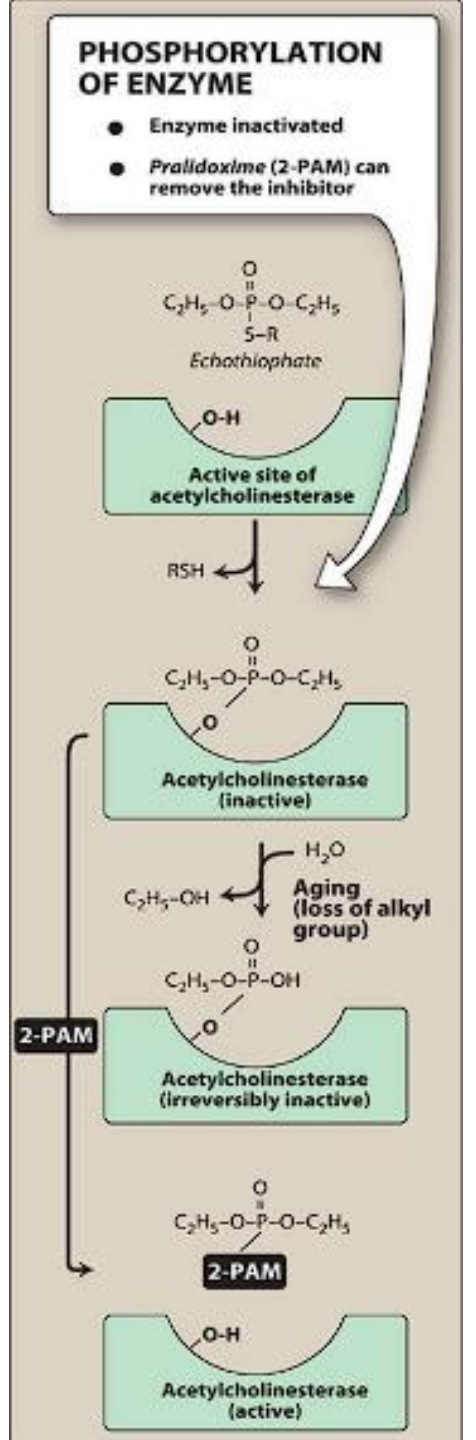
- Progressive loss of cholinergic neurons within the cortex is linked to the memory loss that is a hallmark symptom of Alzheimer disease.
- At best, these compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients.
- Mild to moderate Alzheimer disease.
- Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps.

Anticholinesterase Agents (Irreversible)

- Synthetic organophosphate compounds have the ability to bind covalently and irreversibly to AChE. The result is a long-lasting increase in ACh at all sites where it is released.
- Many of these drugs are extremely toxic and were developed by the military as nerve agents (Sarin). Related compounds, such as parathion and malathion, are used as agricultural insecticides
- Echothiophate : topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. Rarely used due to its side effect profile, which includes the risk of cataracts.
- Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Usually with CNS symptoms.
- Pralidoxime can reactivate inhibited AChE . If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects (can’t penetrate CNS).

‘Aging’ of phosphorylated enzyme

- The phosphate group covalently bind to the enzyme, inhibiting it irreversibly.
- At this state, the phosphate group can be displaced by pralidoxime and the enzyme is reactivated.
- With time, the phosphate group loses an alkyl group, and at this stage the enzyme can not be reactivated.



Cholinergic crisis

- Develops as a result of overstimulation of nicotinic and muscarinic receptors. Usually secondary to the inactivation acetylcholinesterase (AChE)
- In clinical practice, this condition is most commonly seen in:

1. Patients with myasthenia gravis on treatment with high dose acetylcholinesterase inhibitors.
2. Patients after general anesthesia who received high doses acetylcholinesterase inhibitors to reverse the effects of neuromuscular blocking agents, for example, neostigmine.
3. Exposure to a chemical substance that causes inactivation of acetylcholinesterase. Examples of such substances are nerve gas like sarin, tabun, soman and other organophosphates like pesticides and insecticides.

Clinical manifestations

- **Clinical Findings Related to Stimulation of Muscarinic Receptors 'DUMBELS'**

D- Diaphoresis and Diarrhea, **U** -Urinary frequency, **M**-Miosis, **B**-Bronchospasm, **B**ronchorrhea, **B**radycardia, **E** – Emesis, **L** – Lacrimation, **S** – Salivation.

- **Clinical Findings Related to Stimulation of Nicotinic Receptors**

- Muscular weakness, fatigue and fasciculation
- Respiratory muscle weakness

- **Clinical Findings Related to Stimulation of the Central Nervous System**

Seizures, coma, Slurred speech, agitation and restlessness.

Antidotes for cholinergic crisis

- **Atropine (**antimuscarinic**)**

It is an effective agent for the **muscarinic** effect of acetylcholine. It competitively binds to the postsynaptic muscarinic receptor thereby preventing further action of ACh. It is recommended to give atropine until signs of atropinization is present (achycardia, Warm, dry, and flushed skin,Mydriasis)

- ***Oximes***

- For the **nicotinic** effect in cholinergic crisis in organophosphate poisoning. **Pralidoxime** most commonly used.
- Its separates the bonded nerve gas or organophosphate from AChE. There is a window period during which oximes can be given before there is an irreversible bonding of nerve gas to AChE. The aging half-life ranges from two minutes for soman to several hours for sarin.
- Pralidoxime should be given to patients with signs of respiratory muscle weakness or generalized muscular weakness. It should be administered until there is an improvement in muscle weakness. It does not cross the blood-brain barrier hence the central nervous system effect of organophosphate poisoning is not neutralized. This is achieved by using atropine.

- **Other medications in cholinergic crisis**: Seizure and agitation in cholinergic crisis can be treated with benzodiazepine-like midazolam or lorazepam.