Tikrit University
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Cholinergic

Subject name: **Cholinergic**

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SCAN ME

The Autonomic Nervous System

Drugs affecting the autonomic nervous system are divided into two groups according to the type of neuron involved in their mechanism of

1- action. The cholinergic drugs,

2- second group—the adrenergic drugs

Cholinergic agonists

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Neurotransmission in cholinergic neurons involve six steps include:-

1- **synthesis of acetylcholine**:- choline is transported from the extracellular fluid into cytoplasm of the cholinergic neuron by a carrier system that cotransports sodium and can be inhibited by the drug ***(hemicholinium***). Cholin acetyltranserase catalyze the reaction of choline with acetyl COA to form acetylcholine.

2- **Storage of acetylcholine in vesicles**:- the acetylcholine is paged into vesicles by an active transport process coupled to the efflux of protons.

3- **Release of acetylcholine**:- voltage- sensitive calcium channels in the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and release of acetylcholine into the synapse. This release is blocked by ***botulinium toxin***

4- **Binding to receptor:-** acetylcholine released from the synaptic vesicle diffuses across the synaptic space and binds to either postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the ACH. Binding to the receptor lead to a response within the cell such as the ignition of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells as mediated by second messenger molecules.

5- **Degradation of ACH**:- this occurs in the synaptic cleft where acetycholineserase cleaves ACH to choline and acetate.

6- **Recycling of choline**:- choline may be recaptured by a sodium coupled high affinity uptake system that transports the molecule back into the neuron.

III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of acetylcholine (cholinomimetic agents).

Mechanism of action:-

a- muscarinic stimulatant:-

muscarinic receptors (M1-M5).These receptors have been found on ganglia of the peripheral NS. And on the autonomic effector organs,(heart, smooth M. brain, and exocrine glands) ---**M1 found on gastric partial cells**, **M2 on cardiac cells, M3 exocrine and smooth M**.

1- (M1,M3) Receptor ---- G-Protein (Gq, Gs)------- Second Messenger (activation of IP3.DAG) -------- ↓K+, ↑Na+
↑Ca2+ ----------(myosin phosphorylation)
depolarization ,hyperpolarization ,presynaptic inhibition, glandular secretion

2- M2 Receptor ---- G-Protein (Gk, Gi) ------ Second Messenger ↓cAMP increase potassium flux& inhibition of cAMP----- K+, ↓Ca2+ (heart)
↓K+ (sm. muscle) ----- inhibition excitation

B-**Nicotinic receptor activation :-**nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, neuromuscular junction. Action: **depolarization of the nerve cell or neuromuscular end plate bearing the receptor.**

1- muscarinic effect :-

are mainly parasympathomimatic except sweating and vasodilatation, in general are the opposite to those caused by sympathetic stimulation

1- constriction of pupil
2- accommodation for near vision
3- salivation
4- bronchial constriction, bronchosecretion
5- hypotension(bradycardia, vasodilatation
6- increase in GIT motility and secretion.
7- Sweating

2- nicotinic effects:

stimulation of all autonomic gangilia, nicotinic action increase BP due to vasoconstriction and tachycardia.

Cholinergic agonists .

Site of action of cholinergic drugs:

- Autonomic nervous system.
- Neuromuscular junction.
- Central nervous system.
- Non-innervated site: blood vessels, chiefly arterioles that respond vasodilatation through arginine-nitric oxide pathway.

Pharmacologic effect of cholinergic drugs:

- **Eye:** Miosis and stimulate ciliary muscle contraction, eye is accommodated to near vision, and decrease intraocular pressure.
- **Exocrine glands:** Increased secretion from salivary, lachrymal, bronchial and sweat glands.
- **Heart:** Bradycardia, decrease cardiac out put, decrease blood pressure.
- **Bronchi:** Bronchoconstriction and mucosal hypersecretion.
- **GIT:** Increase salivery secretion and stimulate intestinal secretion and motility.
- **Genitourinary tract:** Increase the tone of the detrusor urinae muscle and the drug promote urination.
- **Blood vessels:** Stimulate nitric oxide production from the vascular endothelium that relaxes the underlying smooth muscle.

Drugs which mimic the effects of ACH can be divided into two groups:-

1- **drugs that act directly on the receptor** (nicotinic & muscarinic)
2- **drugs that act indirectly** (inhibit acetylcholinestrease enzyme)

notes:- actylcholine is therapeutically of no importance because of
1- multiplicity of actions
2- rapid inactivation
3- short action.

Drugs direct acting cholinergic agonists:-

These agents are :-

a- synthesis esters of choline**:-(carbacol,bethanchol, methacholin)**
b- naturally occurring alkaloids**: (pilocarpine, nicotine, lobelin).**

Pharmacokinentics:

1- choline esters are :- poorly absorbed and poorly distributed into CNS less active by oral rout , give SC, never IV because of immediate cardiac arrest
2- alkaloids agents:- are well absorbed from most site of administration (lipid soluble)

therapeutic application:-

- bethanchol and carbachol act selectivity on the bowel and urinary bladder.
- While methacholin has selective effect on the heart.

Uses:-

Bethanchol:-used in

1- as prokintic agent (drug which enhances the transit of material through the GI tract)
2- paralytic illus
3- in urology treatment to stimulate the atonics bladder

Carbacol:-because of its high potency and relatively long duration of action . it is rarely used therapeutically ,.
Except in the eye as a miotic agent to cause contraction of the pupil and a decrease in intra-ocular pressure(treatment of glaucoma)

Methacholin:- act chiefly on the heart and produce immediately bradycardia.

Pilocarpine: it is a cholinmimtic alkaloid stimulate both muscarnic and nicotinic receptor it is the drug of choice in both narrow angle and wide angle glaucoma(action lasts up to one day);
Applied topically to cornea ---miosis and contraction of ciliary's muscle.

Also used as antidote to mydriatic agents.(Atropin)

Adverse effect:-

1-especially with bethanchol :-
- bradycardia
- bronchspasm
-hypotension
-nausea, abdominal pain, diarrhea, sweating, salivation

3- carbacol: lead to atrial fibrillation
4- pilocarpine:-CNS disterbences
5- contraindication:- bronchial asthma, peptic ulcer hyperthyroidism, patient at risk for retinal .

indirect acting cholinmimetics (anti-cholinestrease):-

acetylcholinesterase:- is an enzyme that specifically cleaves ACH to acetate and cholin . so terminates its action ,
inhibition of acetylcholisterase enzyme ---accumulation of ACH in the synaptic space------ increasing response at all cholinoceptor of ANS , NM junction and the brain.

They are of two major group:-

- reversible inhibitors (short acting) e.g. physostigamine, Neostigmine
- irreversible inhibitors (long acting) e.g. organophosphorus compounds.

Reversible cholinesterase inhibitors:-

1- physostaigamin: (eserine)

action:- has a wide range of actions (stimulates muscarinic , nicotinic site of ANS, and NM junction: its duration of action is about 2-4h

therapeutic uses:-

- atone of intestine and bladder
- used to treat glaucoma
- treatment over dose of drug with (atropine).
- Improve cogitate function in Alzheimer type of dementia.

Adverse effects:-

With high doses may result in convulsion, bradycardia, skeletal muscle paralysis.

2- Neostigamine:-

less lipid soluble do not pass BBB.

Action:-its actions are more prominent on the NM junction and the GIT than on the CVS and eye, has a moderate duration of action 2-4h

Therapeutic used:-

-to stimulate bowel

-to stimulate urinary bladder

- as antidote for tubercurarine and other competitive neuromuscular blocking agents

- in symptomatic treatment of **myasthenia gravis** which may result due to:-

a- autoimmuno disease caused by antibodies to the nicotinic receptor that bind to ACH receptors of NMjunctions.

b- defect in synthesis or release of ACH.

c- decrease in number of cholinergic receptor (at NM-junction)

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Adverse effects:-

Salivation, flushing, nausea, abdominal pain, diarrhea, bronchospaim.

3- **Edrophonium:-**

Is structurally related to neostigamin, its actions are similar to those of neostigamine except:-

- it is more rapidly absorbed.
- Has a short duration of action (10-20minutes)
- Autonomic effect are minimal except at high doses.
- Therapeutic used:-

Used in the diagnosis of myasthenia gravis ,

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Irreversible cholinesterase inhibitors:

- **Synthetic organophosphate compounds:** Have the capacity to bind covalently to acetylcholinesterase (irreversible inhibition) lead to long lasting increase in acetylcholine at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military nerve agents as turban, sarin, soman although called nerve gas.
- Death due to combination of actions in the CNS and to excessive bronchial secretion and constriction.

Treatment of organophosphate compounds poisoning :-

a- Reactivation of acetylcholinestease as pralidoxime can reactivate of acetylcholinesterase.

b- Other treatment as atropine is administered to prevent muscarinic side effects of these agent. Diazepam is also administered to reduce the persistent convulsion caused by these agents. Oxygen supply and artificial respiration.

Cholinergic antagonist (cholinoceptor-blocking drugs)

They are of two major groups according to the type of cholinceptor:-

1- antimuscarinic drugs.
2- Antinicotinic drugs. Which include.
a- ganglion- blocking drugs
b- neuromuscular blocking drugs.

Antimuscarinic drugs:-
e.g. atropine, scopolamine, Iparatropium.

The principal effect of these drugs is to block competitively the binding of ACH , to receptors at :-

1- postganglionic cholinergic (parasympathetic) endings.
2- Non- innervated receptors on blood vessels
3- CNS.
4- Some have blocking effect at autonomic ganglia., but non blocks the neuromuscular junction at clinical doses .

Atropine (belladonna alkaloid)

Naturally occurring , has high affinity for muscarinic receptors.
Bind competitively ------ preventing ACH from binding to that site.
Atropine is both a central and peripheral muscarinic blocker.
Pharmacokinetics:-
Well absorbed from gut and across the membrane.
Widely distributed after absorption (significant level in CNS within 30-60 minute)
Disappears rapidly from the blood (t1\2 of 2h)
60% of the dose excreted unchanged in the urine.
Its general actions last about 4 h except when placed topically in the eye.
Where the action may last for days.
Actions:-

1- eye:- block all cholinergic activity on the eye ---- mydriasis, unresponsiveness to light and cycloplegia (inability to focus for near vision), in patients with glaucoma, IOP may rise dangerously.
2- GIT : reduces gastric motility, but little effect on gastric secretion.
3- Urinary system: reduces hyper motility states of the urinary bladder .

4- CVS:-

Atropine produces divergent effects on the CVS depending on the dose:-

Low dose:- atropine ---- bradycardia

high dose atropine--- tachycardia

3- exocrine gland :- all secretions except milk are diminished .

4- smooth m. is relax in GIT, bronchial m. urinary bladder.

Therapeutic uses:-

1- ophthalmic----- mydriatic and cycloplegia effects .
2- antispasmodic agent.(renal,biliary colic)
3- Against both tremor and rigidity of parkinsonism.
4- In motion sickness.
5- Antisecretory agent reduce salivary respiratory secretion.(prior to surgery)
6- Useful in bradycardia following MI
7- As antidote for cholinergic agonist.

Adverse effects:-

Depending on the dose :- dry mouth, blurred vision (sandy eye), tachycardia, warm skin ,constipation, effect on CNS (restlessness, confusion, hallucination), Collapse of circulatory and resp. system.---- death.

Contraindications

Glaucoma

Bladder outlet obstruction.

Other antimuscarinic drugs:-

Scopolamine: belladonna alkaloid produces peripheral effects similar to those of atropine, scopolamine has greater action on the CNS and longer duration of action to those of atropine.

Its therapeutic use is limited to prevent motion sickness (prophylactically).

Iapratropium:- useful in treating asthma, and chronic obstructive pulmonary disease in patient unable to take adrenergic agonist.

Hyosine butyl bromide(buscopan) antispasmodic)

Mebeverine(duspataline) useful in GIT disorders.

Pirenzepine:-

It is M1 antagonist--- decrease gastric secretion

Very little side effects, used in treatment of peptic ulcer.

Empironium:- selectivity effect on the urinary bladder

Ganglionic blocker

e.g. nicotine, trimethaphan, hexamethonium
Thus, they are rarely used therapeutically today .
Has not effect on NM junctions, their effects include hypotension, mydriasis, dry mouth, constipation, urinary retention and impotence.

Neuromuscular blocking drugs

e.g. **tubocurarine, galamine, suxamethanium**.
Drugs that block cholinergic transmission between motor nerve ending and the nicotinic receptors on neuro-muscular end – plate of skeletal muscle.

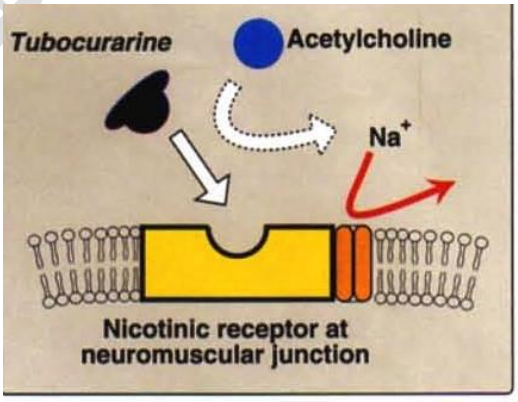
Normal physiology\ Impulse passes down a motor nerve to voluntary muscle--- release of ACH into the synaptic cleft --- activate nicotinic receptor on the membrane of the motor end – plate --- opening (Na) ----- depolarizes the end –plate --- muscle contraction

So\ **these drugs** act either as antagonists (non –depolarizing) or as agonist (depolarizing) at the receptors on the end-plate of NM-junctions.
These drugs have significantly increased the safety of anesthesia to produce muscle relaxation.

Non- depolarizing blockers (competitive).

1- **tubocurarin**e:- introduced into clinical practice in the early 1940s.
mechanism of action:
a- at low doses combine with the nicotinic receptor------ prevent the binding of ACH --- muscle relaxation.
(compete with ACH at the receptor), this action can be overcome by increasing the Conce. Of ACH in the synaptic cleft (by neostigamine)

b- at high doses block the ion channels of the end –plate---- muscle relaxation.



Therapeutic used:-
As adjuvant drugs in anesthesia during surgery to relaxskeletal M. .
Adverse effects:- constipation, urine retention, mydriasis,confusion, bronchospasm, apnea.

2- **Gallamin:-**acts little sooner (2min) than tubrcorarine , does not release histamine, causes tachycardia
3- **Atraurium (t1\2 30 min)**
Advantage in patients with hepatic or renal disease and in the aged
Causes histamine release.

Depolarizing agents:- succinyl cholin (scoline) suxamethonium.

Mechanism of action:-
Attaches to the nicotinic receptor at the motor end- plate---- opening of the sodium channel --- depolarization-- transient twitching of the muscle (fasciculation) (phase 1)
Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses------- the continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked , this causes a resistance to depolarization (phase 11), and flaccid paralysis

Therapeutic uses:-
1- endotracheal intubation.
2- During electroconvulsive shock treatment.

Adverse effects:-Hyperthermia, apnea.