***omCholinomimetric drugs:***

**Cholinergic drugs:**

* The neuron is a communication network that allows an organism to interact with the environment in appropriate ways.
* It can be classified into the CNS&PNS.
* The CNS is composed of the brain and spinal cord.
* The PNS is somatic nervous system and autonomic nervous system.(fig)

**What are the differences between the somatic and autonomic nervous system?**

|  |  |
| --- | --- |
| **Somatic** | **Autonomic** |
| Controls skeletal muscles. | Control smooth muscle of viscera ,blood vessels,exocrine glands,cardiac muscle. |
| Voluntary . | Involuntary. |
| One fiber. | 2 neurons. |

**Autononic nervous system: consist of:**

1. Sympathetic or thoracolumbar outflow.
2. Parasympathetic or craniosacral outflow.(fig)

**Innervation by autonomic nervous system:**

* Most of the organs are clearly innervated by both sympathetic and parasympathetic systems but usually one predominates.
* Some organs as adrenal medulla, kidney, blood vessels, sweat glands and pilomotor muscle receive only from (sympathetic system).

**Neurotransmitters:**

* Chemical substances responsible for communication between nerve cells and between the nerve cells & effector organs.
* Neurotransmitter in sympathetic syetem is noradrenaline and nerves are adrenergic.
* Neurotransmitter in parasympathetic system is acetylcholine and nerves are cholinergic.

**Cholinergic nervous system:**

**Sites of Ach release(fig)**

1. Neuromuscular junction.
2. Autonomic ganglia:all preganglionic nerve fibers of both sympathetic and parasympathetic nerves.
3. Parasympathetic potganglionic.
4. Sympathetic postganglionic fibers to sweat glands.
5. Preganglionic sympathetic nerve to adrenal medulla.

**Chloinergic transmission: (fig)** It consists of:

* Synthesis of acetylcholine
* Storage.

\*N.B: cholinergic nerves are motor(efferent)nerves.

* Release.
* Binding to receptors.
* Metabolism (fate)
* Recycling of the choline.

**1) Synthesis:**

* Choline is transported into cytoplasm of cholinergic presynaptic nerve terminals by carriers.
* Choline+Acetyl CoA Ach + CoA
* Inhibition by hemicholinium,triethylcholine.

**2) Storage:**

* Ach is transported into the storage vesicles by active transport system.
* Inhibition by vesamicol.

**3) Release:**

* Ach is released upon nerve stimulation influx of Ca+2 exocytosis Ach release into synaptic cleft.
* Inhibition by Mg+2,,aminoglucosides.

**4) Metabolism:(**table)

By Acetylcholine esterase.

**Cholinergic receptors:**

1. Nicotinic (central cholinergic) receptors. (located on ganglion)
2. Muscarinic (peripheral cholinergic) receptors. (located on peripheral organs)\

*N.B:[there location depends on type of stimulation].*

**Nicotinc receptors: (fig)**

* Ion channel linked receptors(fast).(type 1)
* Types:1) Neuronal (NN).

2) Muscular (NM)

*N.B:[also depends on its location].*

**Locations of nicotinic receptors:**

1. Autonomic ganglia NN(both sympathetic and parasympathetic).
2. Adrenal medulla.
3. C.N.S.
4. Neuromuscular junction NM.
5. somatic nervous system(since its only a fiber>>>>a way to remember this trick answer)

**Muscarinic (peripheral)receptors:**

* G-protein linked receptors.(type 2)
* Five subclasses(M1-M5)
* M1, M3,M5 are EXCITATORY in function.
* M2, M4 are INHIBITORY in function.

**Locations**: (table)

In ALL effectors organs innervated by cholinergic fibers as:

*CNS has both nicotinic and muscarinic receptors.*

* Smooth muscle(GIT, urinary tract, bronchial muscles)
* Exocrine glands.
* C.N.S.

***What are the actions of cholinergic system activation ?***

* *There is no parasympathetic supply to the ventricles and blood vessels.*
* endothelium of blood vessels respond only to cholinomimetic drugs (exogenous)

1. Nicotinic action.
2. Muscarinic action.
3. CNS.
4. ***Nicotinic actions of ACH* :**
5. **Skeletal muscle :**

* Stimulation muscle fasciculation (twitching) .
* High concentration persistent of depolarization and paralysis .

1. **Ganglia :**

* Stimulation of sympathetic and parasympathetic ganglia .

1. **Adrenal medulla :**

* Release of catecholamines ( A , NA ) .

1. ***CNS actions*:**
2. **Nicotinic actions:**

* ADH secretion from hypothalamus.
* Inhibition of motor fibers.

1. **Muscarinic action** : ACH is involved in memory and arousal.

* Parkinsonism (due to increase in stimulation from cholinergic fibers, and imbalance between dopamine and ACH , ACH is more than dopamine ).
* Dementia of Alzheimer: loss of cholinergic neurons.

1. ***Muscarinic Actions:Table***

**Cholinomimetics = parasympathomimetics :**

These drugs produce actions similar to cholinergic system stimulation.

**Types :**

1. **Direct cholinomimetics** : act by direct stimulation of nicotinic & muscarinic receptors .
2. **Indirect cholinomimetics** : they act indirectly by inhibiting acetylcholinesterase , thus preventing the degradation of ACH .(anticholinestrase drugs).

**Direct cholinomimetics :**

**Classifacation :**

1. **Naturally occuring alkaloids** , eg: Pilocarpine .
2. **Synthetic choline esters** , eg: ACH , Methacholine , Carbachol , Bethanechol

**Mechanism of action of cholinomimetics :**

1. **Muscarinic agonists :**

* Activation of phospholipase C increase IP3 and DAG contraction of smooth muscle ( via M1 & M3 ) .
* Increase cGMP NO release relaxation ( via M3 ) .
* Inhibition of adenyl cyclase ( CAMP ) .
* Opening of K channels hyperpolarization .

1. **Nicotinic agonists :**

* opening of ion channels depolarization

**Pharmacological action of cholinomimetics :** table

**Direct cholinomimetics drugs :**

1. naturally occuring alkaloids :

**Policarpine :**

* **Chemistry:** tertiary amine – basic.
* **Pharmacokinetics**:\*its well absorbed orally.

\*can cross BBB, lipid soluble .

\* Good distribution .

\*not degraded by cholinesterase.

\* Long duration of action .

\*excreted unchanged in urine ( acidifacation of urine will increase the excretion ) .

* **Pharmadynamics:**

1. direct muscarinic agonist mainly on eye and secretions ( saliva, tears,sweat )
2. no nictonic action
3. CNS actions

* **Uses:**

1. Glaucoma (increased intraocular pressure,cholinomimetics are used as a treatment because they cause miosis .
2. xerostomia ( dry mouth)
3. To counteract mydriatics after fundus examination.
4. **Synthetic choine esters:**

Acetylcholine & synthetic choline esters ( Methacholine, Carbachol,Bethanechol)

**Acetylcholine:**

* Quaternary ammonium compound.
* Not absorbed orally (given by injection) .
* Muscarinic and nicotinic agonist.
* Not used due to :\*non selectivity ( b/c it acts on nicotinc & muscarinic receptors )

\*short half life ( cuz it`s degraded by cholinesterase )

**Synthetic choline esters:**Quaternary ammonium compound .

* Methacholine (acetyl βmethyl choline ).
* Carbachol (carbamoyl choline ).
* Bethanechol

**Kinetics :**

* polar
* poor distribution
* cannot cross BBB
* All synthetic cholinesters are resistant in variable degrees to hydrolysis by chloinestrase.

**Pharmacodynamics :**

1. **Muscarinic agonists :**Methacholine- Bethanechol
2. **Muscarinic & nicotinic agonists :**Acetylcholine – carbachol (both have straight structures)

***What re the differences btw Ach and synthetic choline esters?***

Synthetic choline esters are:-

1. More specific.
2. Less or not metabolized by acetylcholinesterase .
3. Have longer duration of action.
4. ***Never*** given I.V or I.M because they might cause severe bradycardia (but can be given subcutaneously ).

**Methacholine(Muscarinic Agonist):**

* Orally or Sc
* Metabolized only by **TRUE** choline-estrase
* Longer duration of action
* More specific
* Muscarinic acts on CVS than GIT & UT.
* **No** Nicotinic action
* Used for: 1-peripheral vascular disease

2-proxysmal atrial tachycardia

**Carbacol (Muscarinic & Nicotinic):**

* **Not** a substrate to Ach-estrase
* Longer duration than Ach
* Both Muscarinic & Nicotinic action
* Muscatinic actions mainly on Eyes, GIT & UT
* Used for: 1-Glaucoma

2-Urinary retention & paralytic ileus.

**Bethanecol (Muscarinic Agonist):**

* Similar to Carbachol but it has **no effect** on Nicotinic receptors
* Orally or SC
* More preferred than Carbachol for Urinary retention & paralytic ileus.

**Uses of Choline synthetic esters:**

* Glaucoma→ Pilocarpine
* Urinary retention→ Bethancol & Carbachol
* paralytic ileum→ Bethancol & Carbachol

**Contraindications:**

1. Bronchial Asthma
2. Peptic Alcer
3. Angina Pectoris