

Title of Lecture: **Acetylcholine (Ach)**

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Sheet no.: **15**

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Acetylcholine (Ach) is an essential neurotransmitter. Its existence in the CNS as a neurotransmitter gives you an idea about its role in certain neurological diseases affecting the CNS *e.g. Parkinson’s disease and Alzheimer disease.*

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* Parasympathomimetic/Cholinomimetic agents meaning their actions look like that of Ach. Directly meaning that they bind directly to Ach receptors.

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* **RECALL!** Indirectly-acting sympathomemtic agents: are those which increase the release of NE or inhibit the metabolism of NE or the activation of NE without binding directly to the adrenergic receptors.
* Likewise, indirectly-acting parasympathomimetic agents do NOT bind Ach receptors but act by inhibiting the enzyme which breaks down Ach (ACHE enzyme).

(Some of them cause reversible competitive inhibition of cholinesterase.)

* We have Tertiary ammonium (nitrogen connected to 3 hydrogens) and Quaternary ammonium (the nitrogen is connected to 4 hydrogens), the significance of this division is that the quaternary ammonium is more polar, more water soluble, do not enter the CNS, they’re given IV and at the same time they’re hydrolyzed very quickly by the enzyme cholinesterase.

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* **Physostigmine** because it’s a tertiary amine could be given orally.
* Reversible anticholinesterase bind anionic site of ACHE.

Not important; don’t worry about on what side they bind to ACHE enzyme.

* Irreversible anticholinesterases are highly lipid soluble so they can be absorbed through the skin. (very dangerous drugs)
* **Sarin**: a nerve gas and is used in wars as a chemical weapon.
* **Malethion and Parathion** are used as insecticides.
* Thus, the importance of getting to know these irreversible inhibitors of cholinesterase lies in the fact that you have to be familiar with their toxicity and how to manage it.

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* The synthesis of Ach is easier than that of NE.
* Following its production, it interacts with specific receptors producing its effects and these effects are very quickly terminated (within milliseconds).

*E.g. any movement you do with your hand causes many Ach molecules to bind to their receptors at the neuromuscular junction producing the contraction of the voluntary muscles involved in this movement and then Ach are quickly being degraded by ACHE enzyme causing the contraction to cease.*

* **Plasma/Pseudo cholinesterase** is present in the plasma, whereas, **Tissue/True cholinesterase** is present in all the tissues.
* Ach is synthesized from **Choline** (nutrient/even categorized as a vitamin/can be taken from food and then is taken up by neurons) and **Acetyl-CoA** (which is synthesized in the mitochondria from glucose which is also a nutrient) by **Choline acetyl transferase**.
* Ach is stored and the released into the synapse where it interacts with the different receptors. (In the case of Ach, there’s no presynaptic receptors unlike NE which has a well identified presynaptic receptors responsible for the high specific reuptake mechanism.)
* Ach binds to receptor to produce its effect and then is quickly metabolized by cholinesterase enzyme.

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* Nicotinic receptors mediate the parasympathetic activity of Ach on the heart, intestines, bronchi…
* Nn: present in the ganglia.

Nm: present at the neuromuscular junction.

* This classification is based on the effects mediated by Ach, which is of high importance in Pharmacology; parasympatholytic drugs which block the muscarinic receptors will not have any effects on Nm or Nm, also, drugs which block Nn will not have any effects on Nm or the muscarinic receptors in the different tissues. (Specific antagonists at the different sites of action of Ach.)

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* Their effects are mediated through second messenger system (IP3, DAG & cAMP) all of them will increase in response to the stimulatory effect of Ach.

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* **RECALL!** The effect of beta adrenergic receptors, especially beta 1, on the heart is increasing its rate and is mediated through cAMP.
* The interaction of Ach with the inhibitory muscarinic receptors, on the heart for example, decreases the level of cAMP by inhibiting Adenylate cyclase leading to bradycardia (abnormally slow heart rate.)

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* Calcium is essential in the contraction of voluntary muscles as well as the release of different neurotransmitters.
* Action potential is generated in response to binding of Ach to its receptors.
* Excess Ach causes:

1. Fasciculation
2. Repetitive contractions
3. Paralysis

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* It’s left to the neurologist to decide what sort of effects Ach does on the CNS (excitatory vs. inhibitory) and what sort of actions are mediated in response to Ach, depending on certain areas in the CNS.
* Epinephrine is released from the adrenal medulla.

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* Ach is ineffective orally and even parenterally and has a very short duration of action.

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* Ach actions are opposite to those of the parasympathetic system.
* Increased GIT motility causes diarrhea.
* You have to be able to reflect Ach actions on the clinical uses of the parasympathomimetic agents and be able to know their opposite; parasympatholytics.

1. Ach increases GIT motility which causes diarrhea, this can be used in the case of constipation /Parasympathomimetic.
2. Ach causes bronchoconstriction, so in patients with bronchial asthma we use Anti-cholinergics /Parasympatholytics.

* Anti-cholinergics are widely used in bronchial asthma and diarrhea.

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* Longer duration of action as compared to Ach because they resist a bit more the degradation by cholinesterases.
* Compensatory effects / Reflexes made by our bodies will be reported as side effects. (any drop in BP is accompanied by increased aldosterone secretions and increased HR)

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* Eye fluid has a synthetic machinery and drainage.
* In glaucoma, there’s an increase in the aqueous humor which increases the intraocular pressure and causes vision complications and that can be managed by decreasing the production of the eye fluid or by enhancing its drainage/excretion.

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* Ach is involved in the contraction if urinary bladder and the relaxation of sphincters.
* **Bathanechol** is effective in evacuating the contents of the urinary bladder after surgery of child birth.
* Preparation of the patient before x-ray or surgery is essential.
* **Carbachol** enhances the movement of the GIT in order to get rid of all its contents.
* **Paralytic ileus** is a common condition occurs after surgeries due to the use of general anesthesia which paralyzes everything including GIT.
* Can be used as a diagnostic tool for **bronchial hypersensitivity/asthma**:

There’s a test that could be used to see whether or not the patient has the ability to develop bronchial asthma.

A patient comes with a difficulty in breathing to the extent that I can’t diagnose this individual being a bronchial asthma patient or not, if he was I have to start him on medications which are bronchodilators with many side effects and if I diagnosed it as steroidal-dependent, I will put him on steroids which are very dangerous drugs that might lead into severe side effects.

Thus, this test allows me to test the patient’s ability to develop bronchial asthma by giving him such agents but in small doses.

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* **Myasthenia gravis (an autoimmune disease)**: production of specific antibodies directed against the nicotinic receptors on voluntary muscles making the binding of Ach to such receptors inefficient.

To enhance the effects of Ach, cholinesterase enzyme inhibitors, like **Physostigmine**, are given and are highly effective in inhibiting ACHE enzyme leading to elevated level of Ach that overcomes the effects of the antibodies.

* For any produced antibody in your body, and by giving its antigen, you can kick the antibody out. (The drug is an antigen.)
* When the drug is a protein in nature, antibodies are produced. The problem with antibodies is that they could lead to a decrease in the therapeutic level of the drug. How to overcome that? By increasing the dose.
* Likewise, here we have antibodies that are directed against the receptors, by increasing the levels of Ach at the neuromuscular junction you can really relieve the manifestations of this disease.
* When the number of receptors drops and the activity of Ach in the voluntary muscle decreases, this will lead to a **progressive weakness in the voluntary muscles.**
* In the case of **Atropine poisoning** we use **Physostigmine**. (Atropine is an anticholinergic drug / the management of over-dose by parasympatholytic agets)

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* **Neostigmine** has more unique actions at the neuromuscular junction.
* Why it is the drug of choice? Because it has more effects on voluntary muscles.
* **D-tubocurarine**: non-depolarizing muscle-relaxant / Ach antagonist.

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* **Edrophonium**: reversible inhibitor to cholinesterases.

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* Low levels of NE and serotonin leads to depression.
* Excess dopamine leads to Schizophrenia whereas its deficiency causes Parkinson’s disease and excess/over-activity of Ach.
* **Rivasigmine:**

1. **Anticholinesterase.**
2. **Orally effective.**
3. **Crosses the blood-brain barrier.**
4. **Has a role in improving the cognitive functions of Alzheimer’s patients.**

EXAM QUESTIONS

* An anticholinesterase has a role in the management of Alzheimer’s disease is: **Rivasigmine**.
* NE is metabolized/deactivated by:

1. MAO
2. ACHE
3. Specific high uptake mechanism
4. **a & c**
5. All of the above

* **BUT, the major metabolic pathway of NE is : C**

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* **Exaggerated Ach effects** are the toxic effects that could be associated with the use of insecticides and chemical weapons.

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* **Respiratory muscle paralysis** leads to **immediate suffocation** which causes **death**.
* **Bradycardia** might lead to **cardiac arrest**.
* **Toxicity with organophosphates leads to immediate death.**

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* The most important and effective management of organophosphate toxicity is by giving **Atropine SC** which is Anticholinergic drug that reverses the manifestations. **(LIFE SAVING!)**
* **Pralidoxime is only effective in the first 12-24 hrs of poisoning** because after that the irreversible inhibition of cholinesterase will take place. **(Only a new enzyme to replace the action if cholinesterase could help.)**
* Insecticides poisoning is very common.

Don’t kill time because time is killing you.

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