**Pharmacology**

**Autonomic Nervous System**

**Lecture10**

**Note**: Most of the time in this lecture, the doctor was only reading from the slides, so I'm going to write *only the extra information* he mentioned 😊 So Please refer to slides in addition to the sheet 😊

**Cholinergic Agonists or Parasympathomimetics**: 

Drugs which produce effects similar to those observed during the stimulation of postganglionic parasympathetic nerve fibers or have actions similar to acetylcholine. These drugs include:

1. **Choline Esters**
2. **Alkaloids**
3. **Cholinesterase Inhibitors or Anticholinesterases**

*Let’s now explain each type 😊*

1. **Choline Esters**

**A) Acetylcholine (Ach):**

Ach is released locally in the synapse. It’s effect is terminated by the action of *acetylcholinesterase enzyme*, so even if we inject Ach in larger amounts or pharmacological doses from an exogenous source, the duration of it’s action will be very short because it will be rapidly hydrolyzed either it is in the synapses or in the circulation (Plasma). This is achieved by the action of both the *specific* *acetylcholinesterase enzyme* (True acetylcholinesterase) & the *non-specific* *acetylcholinesterase* (pseudo-acetylcholinesterase).

*Note*: pseudo-acetylcholinesterases are also known as “False Acetylcholinesterases”
Ach has no therapeutic uses because it has very short duration of action as mentioned above.

**Ach Effects:**

1. Severe Bradycardia
2. Low blood pressure
3. Decrease the contractility of the heart
4. Bronchospasm
5. Increase the activity of the GI & Urinary Tract

Ach used only in experiments to demonstrate the effects of the parasympathetic system. This means that if we gave an antagonist before Ach to see the effect of the Antagonist (Not the effect of Ach), and we noticed that this drug inhibited the effects of Ach, then we can use it in cholinergic system as **“Cholinergic Antagonist”**.

Now we have other Choline Esters that substituted or related chemically to Ach. These drugs **have therapeutic applications** and they include Methacholine, Carbachol, and Bethanecol.

**B) Methacholine**: works mainly on Muscarinic receptors.
**C) Carbachol:** has both nicotinic and muscarinic activity.

*Note:* Drugs that work on specific receptors in specific tissues are better than drugs which work on every part or tissue in the body.

**D) Bethanechol:** In addition to gastric and bladder atony (usually occurs after a surgery or general anesthesia), Bethanechol can be used in Urinary retention to stimulate the contraction of the bladder. *BUT REMEMBER THERE MUST BE NOOO OBSTRUCTION IF YOU WANT TO GIVE THIS DRUG.*

- In most cases, Urinary retention is due to obstruction caused by Prostatic enlargement (Prostatic Hyperplasia), so we should not give Bethanechol in these cases.

- Patients who complain from gastric atony can’t pass feces or even air, so they feel severe pain.

- Bethanechol which is used in Bladder diseases and complications is synthetic, long acting and used orally or subcutaneously.

- If the patient has gastric atony, we shouldn’t give him Bethanechol orally. There’s no point of doing that.

*Please refer to slides to know the molecular structures of the four choline esters*
Alkaloids : Naturally occurring compounds from plants origin, produce similar actions to Ach but inconsistent activity because the origin (Plants) are not standardized.

- Alkaloids were known before Ach.

- Alkaloids include:

  **A) Muscarine:** works on Muscarinic receptors

  Stimulation of Muscarinic Receptors by Ach produces effects similar to those produced by stimulation of the same Receptors (Muscarinic Receptors) by Muscarine, which presents in some species of Mushrooms and can cause poisoning.

  **B) Pilocarpine**

  **C. Nicotine:** Nicotine or any another addicting drug can cause addiction by activation of the brain’s dopaminergic reward pathway (ventral tegment area).

Nicotinic receptors are two types:

1- *Nm (Muscular Type):* presents in neuromuscular junctions.
2- *Nn* (The doctor didn’t mention where it is located but for your information it’s located in autonomic ganglia 😊)

Nn Stimulation can lead to:

1- Higher Heart Rate: The Parasympathetic nervous system is the predominant factor for controlling the heart rate, but stimulation of Nn receptors by Nicotine will lead to over activation or stimulation of the sympathetic nervous system than
the parasympathetic. As a consequence, the heart rate will increase.

2- Vasoconstriction

3- High gastric motility and secretion

4- Increased respiratory rate, due to chemoreceptor activation due to a central action.

5- Medullary emetic chemoreceptor stimulation, leading to nausea and vomiting.

- Nicotine can reduce **Appetite**.

**D) Varnicline** (Trade Name= Chantix) : Used in supporting smoking cessations but it is **less active** than Nicotine.

3. Cholinesterase Inhibitors or Anticholinesterases

These drugs inhibit **Acetylcholinesterase** which destroys Ach, so inhibitors of this enzyme will lead to accumulation of Ach at the synaptic side and consequently working on its receptors.

There are **two types** of Cholinesterase inhibitors:

**A) Reversible**: such as alcohols (e.g. Edrophonium) & Carbamic acid esters (e.g. Neostigmine, Carbaryl)

**B) Irreversible (Organophosphates)**: e.g. Echothiophtae, Soman, Malathion

- Actually, these drugs can be used therapeutically, or they could be only toxins to humans, insects ... etc
Now refer please to Table (7-4) in the slides:

Edrophonium, Neostigmine, Pyridostigmine, and Ambenonium are all used in treating **Myasthenia Gravis**.

**Myasthenia Gravis**: A skeletal muscle disease (Autoimmune neuromuscular disease), leads to weakness of the muscle in spite of the regular activity of Ach.

**Autoimmune disease**: means producing antibodies against own body’s antigens.

In myasthenia Gravis, the antigens are some of the motor-end proteins, so the body starts to produce antibodies against these antigens, binding with the Ach receptors and consequently making Ach ineffective although it is released, because the Ach receptors are blocked 😔

The treatment of Myasthenia Gravis is either to **increase the concentration of Ach** or to **treat the disease with immune drugs**.

**SO MYASTHENIA GRAVIS IS A VERY TRUSTING DISEASE TO SHOW THE ACTIVITY OF THE CHOLENERGIC SYSTEM.**

- **Organophosphates**: 

  Organophosphates are usually toxic, but **Echothiphate** (a type of organophosphates) is the only drug among organophosphates that has **therapeutic use** (that is, in treating Glaucoma).

  Although Echothiphate is so **toxic**, we prefer to use it rather than the other safe drugs (such as Physostigmine & Demecarium) in treating Glaucoma because it **has long duration of action** (approximately 100 hours).
Organophosphates Poisoning:

- As mentioned earlier, Organophosphates are toxic drugs.
- Can be used as *Nerve Gases* in war weapons.
- Used as very potent agriculture insecticides.
- Used in suicidal occasions (e.g. Lanate).
  - Inhibit the enzyme and cause accumulation of Ach at all sites including central nervous system (CNS).

Why are organophosphates so toxic?

Because they are very lipid soluble, so they can be easily absorbed through all parts of the body and deposit anywhere.

Treatment of Organophosphates poisoning:

- We have to wash all the body because these drugs are very lipid soluble and can be absorbed at any part of the body.

- Using Atropine:
  
  Atropine is a very short acting drug. This means that we need to give it in large or frequents doses (100-150 mg Ampoule) in the cases of Organophosphates poisoning. Atropine is also used in Bradycardia & Anesthesia.

  We continue to give atropine until we reach “Atropine Poisoning”. Why? O.o
  - Because Atropine Poisoning is less dangerous than the hazardous organophosphates poisoning 😊

  Atropine is a parasympatholytic drug. In other words, it’s a muscarinic antagonist.

I’m really sorry for any Mistake. I tried my best 😊

Your Colleague: Abd Alrahman Abu-Naba’h