CENTRAL NERVOUS SYSTEM

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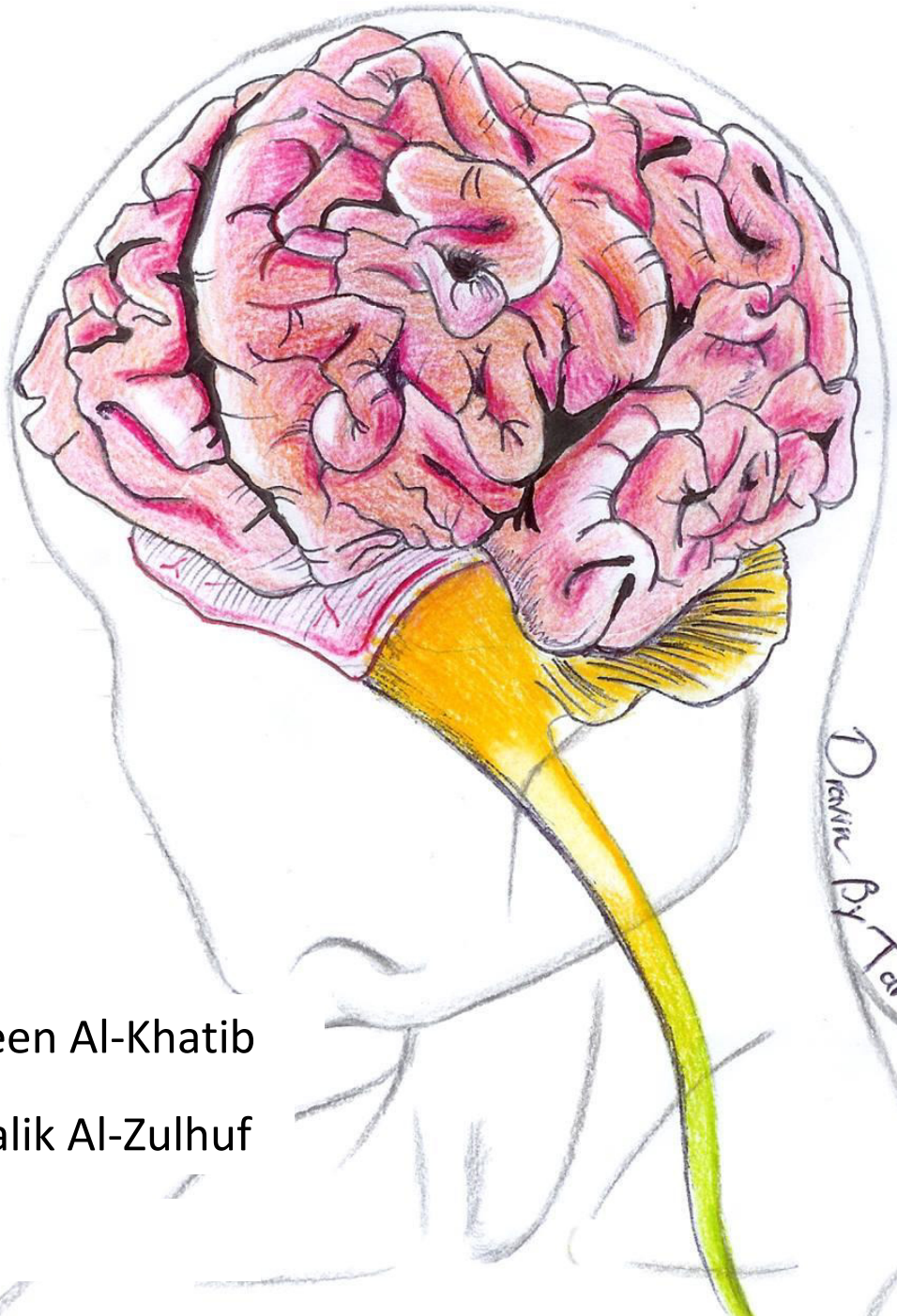

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Lec #: 11

Drugs used in treating Parkinson & Alzheimer

-Let us revise some main points first:

PARKINSON

:: Drugs that are used to restore dopamine in Parkinson

-In the previous lecture, we started talking about these drugs & we talked about **Levodopa:**

-A precursor of dopamine that is used to restore dopamine levels in the brain, since dopamine can't cross the blood brain barrier.

-In the new patient, the therapeutic response is consistent.

-In advanced cases, the number of neurons decrease and fewer cells are capable of taking up Levodopa and convert it to dopamine for subsequent storage and release. Subsequently, motor control fluctuation developed. The phenomena that is called "wearing off".

-Relief provided by Levodopa is only symptomatic, and it lasts only while the drug is present in the body.

- Large doses are required, because much of the drug is decarboxylated to dopamine by dopamine decarboxylase in the periphery, resulting in side effects. And to solve that, Levodopa is combined with Carbidopa, which is a dopamine decarboxylase inhibitor that does not cross the blood brain barriers.

- Carbidopa, diminishes the metabolism of the Levodopa in the peripheral tissues, and increases the availability of Levodopa to the CNS.

Let us now start with the new lecture to continue :

Levodopa & Carbidopa

- In two third of patients, the combination of these two drugs is to reduce the severity of the disease in the first few years, then a decline in response is experienced during the third to fifth year of therapy ("**wearing off**").
- **Adverse effects of these drugs which are produced by dopamine which is restored by them:**

1-Nausea & vomiting:

-Dopamine may stimulate the emetic center & causes nausea & vomiting. But fortunately, within the first month, there will be **tolerance** toward the emetic effect of dopamine.

2-Orthostatic hypotension:

-Also, within the first two months, there will be **tolerance** toward this effect.

-We conclude that the patient within the first two months **will not** suffer from these adverse effects **(nausea, vomiting (emesis), orthostatic hypotension)**. He/ she will develop these effects only if **high doses** of these drugs are injected.

3-Tachycardia and Ventricular extrasystolic :

-So we should not give these drugs for patients who suffer from **angina pectoris**.

4- Hallucination, confusion and abnormal involuntary movements, dyskinesia:

-The **most common** adverse effects, which are produced by over activity of dopamine in the receptors in the brain (too much signal transduction).

***Hallucination, confusion :**

-These effects represent the **positive symptoms** of **psychosis.**

-A big problem about **dopamine over activity** is that it causes what we call "**Impulsive-compulsive activity**"**;** a psychiatric disorder in which the patient becomes wild (mad & uncontrolled)**,** & can harm anybody. It happens with **Levodopa & Carbidopa** in about **6%** of the population.

-Other drugs used to treat **Parkinson's disease** such as **D2 & D3 agonists** which have **a higher efficacy** than **Carbidopa & Levodopa** also produce the "**Impulsive-compulsive activity**" in **20-30%** of the population (**more common** than **Carbidopa & Levodopa**).

-However, the **main** drugs to use in treating **Parkinson are Carbidopa & Levodopa** because they produce **less** side effects of **hallucination & confusion.**

***Abnormal involuntary movements, dyskinesia :**

-By activating D2 receptors too much & the dopaminergic motor pathways.

-Now suppose we gave a patient a combination of levodopa & carbidopa. After three years of giving these drugs, the "**wearing off**" response started. What should you do to increase the level of dopamine?

-We do one of these mechanisms:

1-We give the patient **D2 agonists**.

2-We give the patient **MAO-B inhibitors**. (**MAO-B** is the one responsible for dopamine metabolism), thus increasing the level of dopamine in the substantia nigra & producing more effect. One of those MAO-B inhibitors is a drug called **Selligiline**. Definitely, we can't start with this drug from the beginning to treat Parkinson, because we need dopamine from outside & this drug only inhibits the metabolism of dopamine which is already present inside. So it's only an **add on drug used to delay** the "**wearing off**" **phenomena**.

-From the slides :

-Selligiline is a drug used for the treatment of early-stage Parkinson disease.

-Selegiline exhibits little therapeutic benefit when used independently, but enhances the action of Levodopa, and when administered together, Selegiline substantially reduces the required dose of Levodopa.

-When given at high doses, it places the patient at high risk of **hypertension**; this is because it inhibits MAO, so inhibiting the metabolism of norepinephrine & epinephrine. Actually, what happens here is that this drug at high doses loses its selectivity, so it starts to inhibit **MAO-A** (the one responsible for metabolism of **epinephrine, norepinephrine, serotonin & dopamine**) in addition to **MAO-B**.

3-We give the patient **catechol-O-methyl transferase** (**COMT) inhibitors**; such as **Entacapone** & **Tolcapone (add on drugs),** so when the patients takes them with **Levodopa & Carbidopa,** there will be a **decrease** in the plasma concentration of 3-O-methyldopa (a major metabolite of Levodopa) , thus **increasing** the central uptake of **dopamine**.

-From the slides :

-When peripheral **dopamine decarboxylase** activity is inhibited by **Carbidopa**, a significant concentration of 3-O-methyldopa is formed and competes with **Levodopa** for active transport into the CNS. So they interfere with the transportation, thus; building up more Levodpoa within the CNS.

-Both of these agents have been demonstrated to reduce the symptoms of "wearing off" phenomena seen in patient on Levodopa-Carbidopa.

- The adverse effects of COMT inhibitors :

1-Diarrhea.

2- Postural hypotension.

3-Hallucination.

4-Sleep disorders.

5-Hepatic necrosis : produced by **Tolcapone**, so it's not used anymore & the major drug which is used today is **Entacapone**.

-**Note** : We can give the patient a combination of all of the mentioned drugs. Ex : we give him carbidopa+levodopa+selligiline+entacapone.

Dopamine receptors agonists

- **This group includes:**

1- Bromocriptine and Pergolide. (the old ones).
2- Ropinirole and Pramipexole. (the new ones).

-The doctor will focus on those two drugs: Bromocriptine & Ropinirole.

Bromocriptine & Ropinirole

-They are **D2** agonists.

- They have **longer** duration of action than that of Levodopa; which is an advantage of these drugs, thus have been effective in patients exhibiting fluctuation in their response to Levodopa, so if the patient has started the "wearing-off" phenomena, you can give him these drugs.

→**Controversial issue** : Some suggests starting with D2 agonists as a treatment to delay the "wearing-off" response, but the doctor said that most of the pharmacy associations suggest starting with **Levodopa & Carbidopa** to treat Parkinson.

-Initial therapy with the newer agents is associated particularly with less risk of developing dyskinesias and motor fluctuations in comparison to Levodopa & Carbidopa. However; they have more tendency to produce **hallucination** (**20-30%** of the population). – remember the impulsive-compulsive disorder-.

-**Their side effects**: similar to that of Levodopa. However, the hallucination, confusion are more common, while dyskinesia is less frequent & serious cardiac problems may develop, particularly with patients with myocardial infarction.

Amantadine

-Antiviral drug; effective in treating influenzae-A viral infection.

-As anti-parkinson action, it increases in the release of dopamine from the substantia nigra, blocks cholinergic receptors, and blocks some of the NDMA glutamate receptors.

-Adverse effects:

1- Restlessness.

2- Agitation.
3- Hallucination.
4- Dizziness: a very common side effect; occurs in patients who are greater than 60 years old (polypharmacy patients).

- It's less officious than Levodopa and tolerance develops more readily. However, it has lower side effects.

-It's used sometimes at the very early stages of the disease to delay the usage of Levodopa+Carbidopa, & it's used rarely in very special cases.

:: Drugs that are used to antagonize the excitatory effect of cholinergic neurons in Parkinson

Antimuscarinic agents

1- Benzotropine.

2- Biperidine.

-Both are similar, although individual patient response more favorably to one drug, so we can give them together.

-They block the acetylcholine in the brain by blocking the muscarinic receptors which leads to blockage of the cholinergic transmission and production of effects similar to rise of dopaminergic transmission, so they

balance between the dopamine & acetylcholine levels. - Blocking of the cholinergic transmission produces effects similar to augmentation (rise) of dopaminergic transmission-.

-They have much less efficacies than Levodopa and play only an adjuvant role in anti-parkinsonism therapy.

-Their side effects:

1- Mood change.
2- Dryness of the mouth.
3- Constipation; by interfering with the gastrointestinal peristalsis.
4- Urinary retention.
5- Visual problems (blurred vision).
6- They are contraindicated in glaucoma.

-Some last notes about treating Parkinson:

-Start with Levodopa & Carbidopa & when the "wearing-off" response begins, give COMT inhibitors or MAO inhibitors then try giving the dopamine agonists drugs. However, some doctors start with the dopamine agonists, but the doctor said that if we start with them the receptors will lose their activity after a period of time.

-Anti cholinergic drugs don't have an important role in treating Parkinson. We may give them if the patient can't tolerate the dopaminergic drugs.

ALZHEIMER

-Is a disease characterized by progressive loss of cholinergic neuron and, presumably cholinergic transmission within the cortex which leads to the memory loss that hallmark symptoms of Alzheimer disease & it may progress to hallucinations.

-Alzheimer is becoming more popular in Jordanians, because they live longer. And it happens with people who are greater than 65 years old.

-Pharmacological intervention for Alzheimer disease is only **palliative** (calming) and provides modest short-term benefit. There is no definitive treatment actually for Alzheimer.

-None of the current therapeutic agents alter the underlying neurodegenerative process.

-The aim of the treatment is to increase acetylcholine, since it's caused by decreased levels of acetylcholine.

Remember => Cholinergic drugs are of two types:

1-Direct : by stimulating the cholinergic receptors. Ex: Bethanechol.

2-Indirect : by inhibiting choline esterase. Ex: Neostigmine & Physostigmine,

::Drugs used in treating Alzheimer

-Acetylcholine esterase inhibitors

-We need drugs that are effective in **crossing the blood brain barrier**:

1- Donepezil.
2- Galantamine.

-They inhibit the metabolism of acetylcholine by inhibiting choline esterase thus increasing the level of acetylcholine.

-At best these agents provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer disease. –They are not very effective.-

-Their adverse effects:

1. Anorexia.
2. Muscles gramps.
3. Diarrhea.

-NDMA receptors antagonists

-Over stimulation of glutamine receptors, particularly of the NMDA type, has been shown to result in excitotoxic & killing effects on neurons, and is suggested as a mechanism for neurodegenerative processes.

-Antagonists of NDMA glutamine receptors are often neuroprotective, preventing the loss of neurons following ischemic and other injuries.

-Example on these drugs is **Memantine** :

-An antiviral drug.

-It has shown to prevent or slow the rate of memory loss in Alzheimer dementia, even in patient with moderate to severe cognitive losses.

-It is well tolerated, with few dose related adverse effects, which include **confusion** and **restlessness**.

→Always remember that there is no treatment for Alzheimer disease, we only treat the symptoms which will lead to little improvement.

Brain stimulants

-Why do we need to stimulate the brain?

1- In order to increase the concentration of the patients such as in ADHD disease. (**Attention-deficit hyperactivity disorder**).
2- Some brain stimulants may lead to loss of appetite in order to lose weight.
3- In order to wake & alert a person who has sleepless disorders & sleeping problems, such as in **Narcolepsy**; a chronic neurological disorder involving the loss of the brain's ability to regulate sleep-wake cycles, the patient might sleep suddenly while talking with someone.

4- Enhancement of motor activity. Horses were injected with CNS stimulants to speed up their running.
5- Euphoria. Ex: the use of the drug **Ecstasy** (amphetamine) in night clubs to be able to dance all night.

→CNS stimulants are addictive & they produce euphoria with high doses. Ex: cyclidine (الكبت).

-Examples of these stimulants:

1. **Nicotine** (smoking).
2. **Methylxanthine** such as **Caffeine & Theophylline** (Anti-asthmatic drug).
3. **Cocaine.**
4. **Amphetamine.**
5. **Atomexitine.** (Anti-depressant); causes reuptake inhibition of norepinephrine.
6. **Modafinil, Methylphenidate** : they have been abused.

-Signs & symptoms indicating using these stimulants:

1. Mood elevation.
2. Increasement in the motor activity.
3. Increasement in the alertness.
4. Decreasement in the need for sleep.
   →In case of overdose, they lead to convulsion and death, so they are not great drugs by themselves, they can be easily overdosed & many cases of death result from Amphetamine-Ecstasy.
5. Meth mouth (severe tooth decay-black teeth) by **Methamphetamine;** a very common drug in America.

-Therapeutic indications to use these drugs:

1-Obesity : because of their effect in decreasing the appetite, but they have been misused & nowadays they are not used anymore for this purpose.

2-Attention Deficit Hyperactivity Disorder (ADHD) : the most important & common therapeutic indication to use them, & it's the disorder in which the patient lacks the ability to be involved in any single activity for longer than a few minutes, so we give these stimulants to increase the patient's concentration.

3-Narcolepsy: it's a relatively rare sleep disorder, which is characterized by uncontrollable bouts of sleepiness during the day.

-Contraindications of these stimulants:

1- Anorexia.
2- Insomnia.
3- Asthenia.
4- Psychopathic personality, a history of homicidal or suicidal tendencies.

Amphetamine

-Mechanism of action: reuptake inhibition of norepinephrine & dopamine into the presynaptic neuron & increase the release of these monoamines into the extraneuronal space.

-Clinical uses: 1-Narcolepsy. 2- ADHD.

-BUT we don't use it today because it's **adverse** effects:

1-Cardiovascular : Hypertension because of the increasment in norepinephrine. It occurs in 7-22% of patients including pediatric patients.

2-Endocrine : Weight loss because of the loss of appetite.

3-Gastrointestinal: Abdominal pain, Loss of appetite, Xerostomia.

4-Neurologic: Headache (25-30%), Insomnia, Nervousness, Euphoria.

Methylphenidate

-It has CNS stimulant properties similar to those of amphetamine and may also lead to abuse, although its addictive potential is controversial.

-It is taken daily by 4-6 million children in the USA for ADHD, better than amphetamine.

-It's a more potent dopamine transport inhibitor than cocaine, thus making more dopamine available.

-It has less potential for abuse than cocaine, because it enters the brain much more slowly than cocaine and, does not increase dopamine levels as rapidly.

→ Adverse effects:

- GIT effects are the most common; abdominal pain and nausea.
- In seizure patients, methylphenidate seems to increase the seizure frequency, especially if the patient is taking antidepressants.

➔ Remember :

- **Amphetamine**→misuse is common, small doses of Amphetamine can lead to euphoria, fatigue…etc.
- **Methylphenidate**→it enters the brain slowly, so it needs time to produce euphoria, fatigue…etc. Anxiety & other nervous symptoms are not very clear.

Nicotine

-It's the active ingredient in tobacco. Used in smoking cessation therapy.

-Mechanism of action:

- Low doses: ganglionic depolarization-stimulatory effect.

- High doses: ganglionic blockade-inhibitory effect, so it has a toxicity effect & can lead to death.

-Actions of Nicotine:

→Central nervous system effects

- Low doses (1-2 mg): euphoria, arousal, relaxation, improves attention, learning, problem solving and reaction time.
- High doses (around 20 cigarettes/hour): CNS paralysis, severe hypotension (medullary paralysis).

→Peripheral nervous system effects:

- **Sympathetic** : Stimulation of sympathetic ganglia and adrenal medulla which will lead to increase heart rate & blood pressure which may increase the stiffness of blood vessels & make them more susceptible for atherosclerosis. (harmful in HTN patients).

The doctor thinks that 80% of stroke patients are smokers.

- **Parasympathetic**: Stimulation of parasympathetic ganglia which will lead to increase motor activity of the bowel. At higher doses, blood pressure falls & activating ceases in both GIT and bladder.

-Adverse effects:

1- Irritability and tremors.
2- Intestinal cramps, diarrhea.
3- Increase HR & BP.
4- Withdrawal symptoms: nicotine is an addictive substance; physical dependence develops rapidly and can be severe. For people who are willing to stop smoking, we deal with their physical dependence by offering nicotine patches that release nicotine in gradually lowered doses.

من أكتر الأشياء اللي ممكن تنجح فيه بسهولة بدون ما تضلك تحاول وتفشل، تحاول و تفشل لحد ما تنجح هو الأخلاق واللي ما عنده أخلاق أي شغلة هو ناجح فيها رح تكون نجاح مؤقت لو شو ما طول آخرته ينتهي بالفشل.

GOOD LUCK

Sireen