CENTRAL NERVOUS SYSTEM

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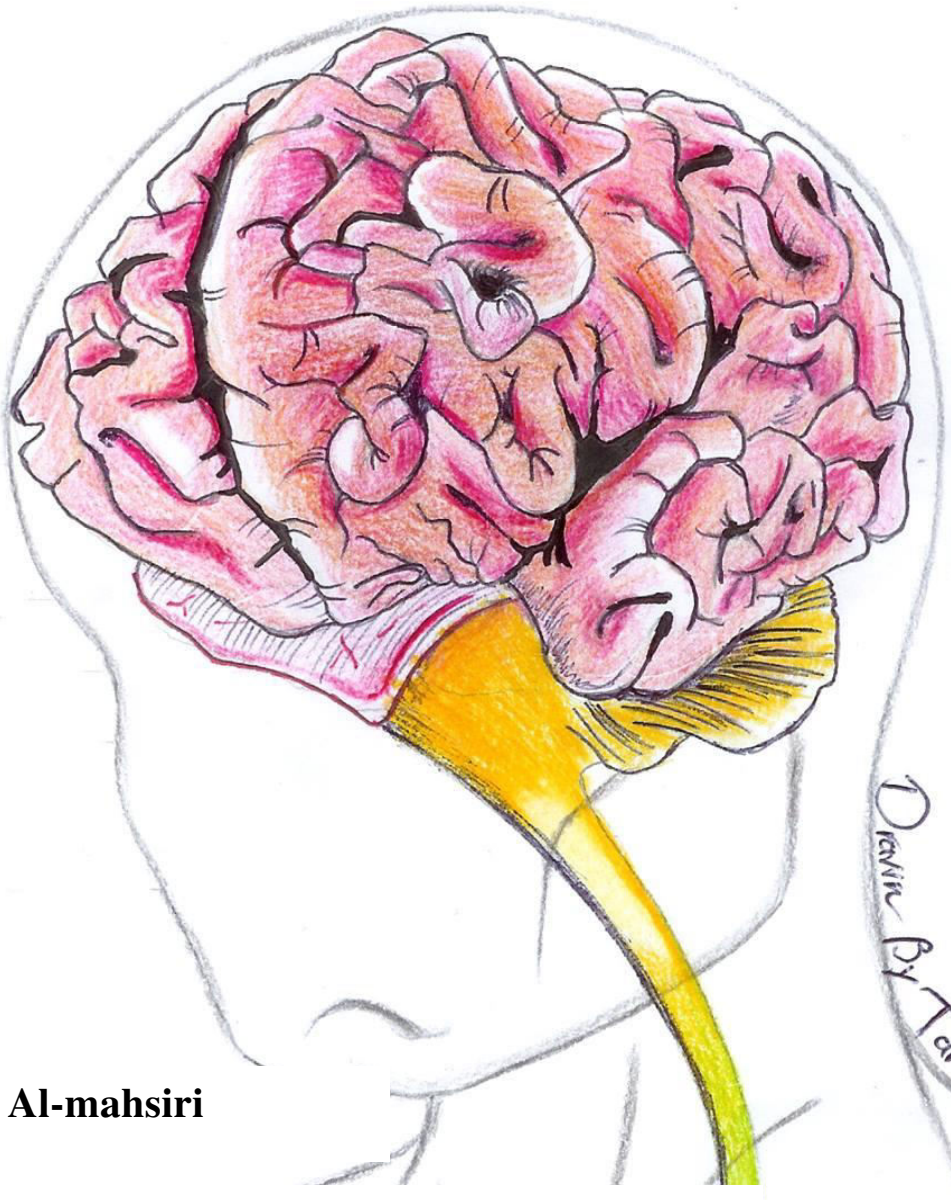

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Lec #: **6**

Local anesthesia

We use local anesthetic drugs to locally anesthetize our patient. These drugs are mostly used in dental clinics, as we sometimes have to locally anesthetize around the teeth. How do we do that? By blocking Na channels.

We took anti-arrhythmic drugs last term, one of them is **lidocaine**, which is the drug of choice for post-myocardial infarction if the patient has tachyarrhythmia especially left ventricular tachyarrhythmia, because in post-myocardial infarctions there is leakage of Na ions through cells, which causes arrhythmia, so we use lidocaine to block Na channels.

Local anesthetic drugs block the initiation and spread of action potential in nerve fibers by preventing the voltage-dependent increase in Na conductance. So we inhibit initiation and progression of the sensation. Neurons responsible for pain and temperature sensations are slow-conducting, and local anesthetic drugs basically inhibit impulse conduction of these slow-conducting neurons.

If you increase the dose very much, local anesthetics may affect motor neurons, but generally speaking they don't cause reduction in conductivity of motor neurons. (From the internet: Fortunately, the sensation of pain is usually the first modality to disappear; it is followed by the loss of sensations of cold, warmth, touch, deep pressure, and, finally, loss of motor function, although variation among patients and different nerves is considerable.)

Mechanism of action of local anesthetics:

They work in two ways: (from the slides)
1- By acting non-specifically to stabilize the membrane
2-By specifically plugging Na channel → most important

When the patient has inflammation, the condition of inflamed tissue is acidic, and when the patient has hypoxia this also produces acidic conditions in the patient.

If the patient is hypoxic (no enough O2 reach the tissue) the acidity will be high and pH low.

When the pH is low, weak bases are more ionized → polar compounds → the drug cannot cross the membrane → drug is not active.

Keep in mind that local anesthetics bind Na channels from the inside, so they have to cross the cell membrane of the neuron and if they're ionized, they can't do that. So sometimes when you go to the dentist, they give you three injections of lidocaine because you have inflammation, but if you don't have inflammation, only one is enough.

Inflammation increases acidity → and that decreases the activity of local anesthetic drug , requiring you to give the patient more and more of local anesthetic drugs to desensitize the area.

Some doctors mix lidocaine with bicarbonate (base) to increase pH → we reduce ionization → we have more lipophilic drugs able to cross the membrane.

There are many local anesthetics but we don't need to memorize them, we need only to know lidocaine.
All those local anesthetics are derived from cocaine, and all of them have similar mechanisms of actions but they differ from Cocaine in two thing: 1- pKa 2- lipophilicity.

Some of them are more lipophilic so they can cross the membrane quicker and they have lower pKa.

Differences in pKa and lipophilicity give us ideas about how long these drug work; some are long-acting, some are short-acting. We use them depending on the duration and type of procedure.

We have to know these three drugs: **procaine, lidocaine, tetracaine** (all 3 have the same action)

In all cases (except in spinal anesthesia and epidural anesthesia) we mix local anesthetic drug with **epinephrine** to prolong the action of the drug .

Na channel blockers are toxic drugs because they are:
1- Depressors of the heart
2- Vasodilators
3-Decrease conductivity of the nerves
4- Increase excitability of CNS

So they affect the brain, vascular smooth muscle, heart and nerves.

We reduce the effect by mixing all anesthetic drugs with adrenaline to cause sustained release of the drug to the systemic circulation which doesn't give chances toward a high peak, which means they reduce side effects.

We will move to talk about:

Nerve block:

-Injected locally to produce regional anesthesia (e.g. dental and other surgical procedure.)
-Local anesthetics are injected subcutaneously around sensory nerve endings, useful in minor injury.
Infiltration anesthesia can be produced with **0.25_0.5 %** aqueous solution of lidocaine or procaine (usually with co administration of adrenaline), **adrenaline** causes vasoconstriction and reduces side effects.

Topical agent:

-Local anesthetic is applied directly to mucous membrane such as those of the

conjunctiva, nose, throat or urethra.
-Usually we use tetracycline, lidocaine and procaine.
-Onset anesthesia takes about 20 seconds, and duration of action is about 8 minutes.
-We use high concentrations (**2-5 %**)
-We use it when the patient is afraid of oral injections, we give topical anesthesia to make desensitization. Also effective in burns, some eye drops are also considered topical agents.

Injection agent:

-Intravenous regional injection (local anesthetics are basically injected intravenously)
- local anesthesia injected IV distal to a pressure cuff to arrest blood flow.
-Remains effective until the circulation is restored
-Used for limb surgery (knee/hip replacement surgeries for example.)
-mainly we use lidocaine (ligocaine) and prilocaine .

Spinal anesthesia:

-Local anesthesia injected intrathecally into CSF of subarachnoid space to act on spinal root and spinal cord. (So intrathecal administration is injection into the spinal canal, more specifically into the subarachnoid space so that it reaches the cerebrospinal fluid (CSF) and is useful in spinal anaesthesia, chemotherapy, or pain management applications.)
-No need to use adrenaline (space is limited, no blood supply)
-We can use opioids (Fentanyl if the duration of the surgery is short, and morphine if it's quite long.)
-Used for surgery to abdomen, pelvis, leg, when general anesthesia not appropriate.
-Mainly lidocaine and tetracaine.

Epidural injection :

- Injection of local anesthetic to spinal column but outside the dura matter,

Women often have an epidural during childbirth.
-Used during labor → **balanced anesthesia**; uterine contractions still occur, but she doesn't feel any pain (Unlike in spinal anesthesia, where anesthesia might interfere with uterine contractions.)
-We don't use spinal injection during labor because it even affects motor functions.
_Side effects in epidural are less than the spinal.
_Main side effect is hypotension (they cause vasodilation), might result in cardiac arrest/arrhythmias. Overdoses of Lidocaine might also cause heartblock.

Depression:

-It's important to know the state of mental health of patients because when patients are depressed, we don't use any drug that causes depression because that drug has many side effects. Some patients are schizophrenic, so we don't use that drug because they cause involuntary movement.

- We really need to understand them very well, and this topic is very complex and we have a limit to understand that topic. Obama funded a billion project to explain the brain map.

-The optimal use of antidepressants requires a clear understanding of their mechanism of action, pharmacokinetics, potential drug interactions and the deferential diagnosis of psychiatric illness.

-Depression is a combination of many diseases, some of them are genetic and other is not genetics and we will hear a lot of thing about this.
-Genetic mean that people have tendency towards depression while others have no tendency to develop depression. (10 % genetic … 90% not genetic …)

- Depression is currently the fourth most significant cause of suffering and disability worldwide, and the most common cause in America. In Jordan there is

increase in depression and schizophrenia.
-Schizophrenia is more common in males, whereas depression is more common in females (4:1)
-Depression will be the second most disabling human condition by the year 2020.
-Dopamine is a more lady related-issue .. E.g. delivery.

There are many theories about depression:
1- exogenous or endogenous
2- personal or induced
3- genetic or environmental

Depression is due disturbances in neurotransmitter levels (Dopamine, Serotonin, and norepinephrine.)
-Dopamine: attention, pleasure, emotion, reward, motivation, movement.
-Serotonin: regulate mood, sleep, emesis, sexuality, appetite, aggression
-Norepinephrine: alertness, observance, daydreaming hear, stress
There is overlap between functions of these NT.

Symptoms:
1- cognitive
- thought of helplessness, poor confidence, negative thought.
2-emotion
- feeling sad, unable to feel pleasure, irritability
3- psychosis
-decreased libido, sleep changes, appetite change
- we don't have suicide in Jordan, and depressed patients might attempt to suicide. Depression might accompany mania and this is when it's called bipolar disorder. Depression basically means sitting in the corner and not wanting to continue living.

We need to learn two things:

1- Depression is increasing (Anti-depressants are the second most commonly prescribed drugs. Alprazolam, a hypnotic, is number one.)

2- Prescription of drugs is increasing, depression is very popular.

There are many theories about depression:

1- Monoamine hypothesis of depression:

-The monoamine hypothesis grew originally out of association between the clinical effects of various drugs that cause or alleviates symptom of depression and their known neurochemical effect on monoaminergic transmission in the brain.

-Monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic NT.

-The chronic activation of monoamine receptor by antidepressants appears to increase in BDNF (brain levels of derived neurotrophic factor) transcription, and one of the weaknesses of this hypothesis is the fact that **amine levels increase immediately with antidepressant use, but maximum beneficial effect of antidepressant are not seen for many weeks**.

-The response is after 3-4 week of use this drug.

The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects, you're not just increasing NT levels, you're also increasing BDNF levels by increasing their expression. That's why monoamine oxidase inhibitors need a long time to start working.

2-Neurotrophic hypothesis:

-Depression appears to be associated with a drop in brain levels of derived neurotrophic factor (BDNF) level in the CSF and serum as well as with a decrease in tyrosine kinase receptor B activity.

-BDNF is thought to exert its influence on neuronal survival and growth effect by activating the tyrosine kinase receptor B in both neuron and

glia.
-Animal and human studies indicate that stress and pain are associated with a drop in BDNF level and that this loss of neurotrophic support contributes to atrophic structural change in the hippocampus and perhaps other areas such as the medial frontal cortex and the anterior cingulate.
-Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate and medial orbital frontal cortex.
-This theory is better than monoamine hypothesis and actually the monoamine hypothesis works after 2-3 week because it needs 2-3 week to increase BDNF levels.

-Your job is to increase BDNF levels so that the hippocampus and neural connections of the patient goes back to normal.

-We use drugs that increase levels of Dopamine, Noradrenaline and Serotonin. Examples of these drugs are Sertraline, Escitalopram, etc. There is a very long list in the slides and the doctor skipped it.

-Most anti-depressants have similar efficacies but they differ in their side-effects. We'll talk about the groups of anti-depressants in more detail the next lecture.

-From Wikipedia: An **autoreceptor** is a receptor located on the neuron (terminals, soma, and/or dendrites), and the function is to bind a specific ligand (such as neurotransmitters or hormones) released by that same neuron. The autoreceptor is mainly used as a feedback mechanism to monitor neurotransmitter synthesis and/or release. (Found at the pre-synapse, cause feedback inhibition of Noradrenaline, Serotonin and Dopamine.) This will be explained better next lecture.