CENTRAL NERVOUS SYSTEM

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- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
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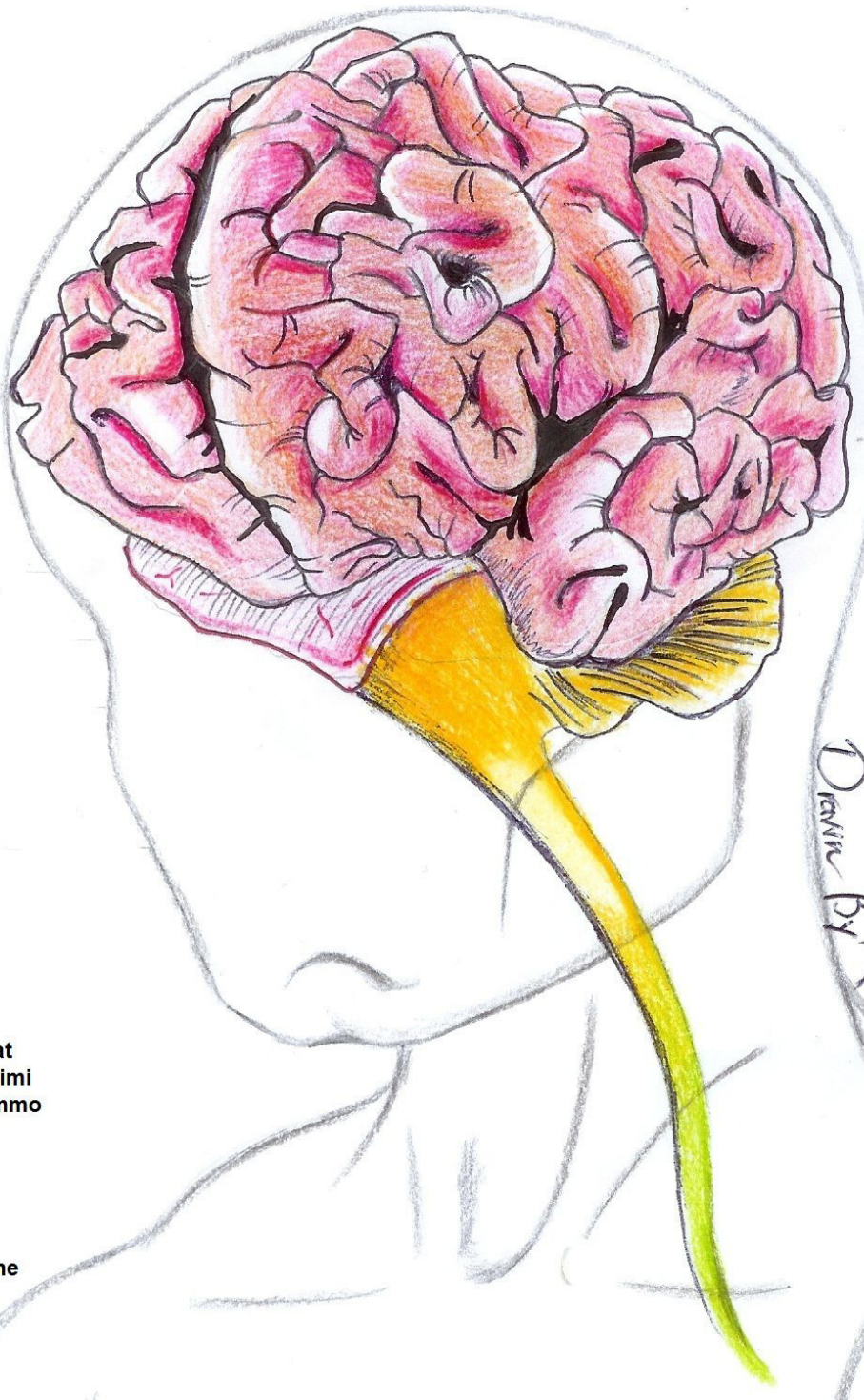

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Lec # : the missed one

Intravenous anesthetics

Recap and continuation of the previous lecture

Yesterday we talked about the concept of balanced anesthesia and we compared it with monoanasthesia and we said that if we want to induce general anesthesia in a patient we must:

1- Induce analgesia
2- Induce muscle relaxation
3- Induce a state of unconsciousness

In monoanasthesia one agent can produce all of those functions however we need a very large concentration of that agent which predispose the patient towards **respiratory depression and coma** however in general anesthesia we use multiple drugs to achieve all of those functions which reduces the dose needed for each individual drug therefore decreasing the risk of respiratory depression and death. **In conclusion the mortality rate with balanced anesthesia is less than monoanasthesia .**

We talked about four drugs used in anesthesia:

1- Halothane: **Hepatotoxic** , increase the sensitization of the heart toward catecholeamines causing **cardiac arrhythmia** and it produces rapid **hypotension** .

2- Enflurane: we moved from halothane towards this drug however they found that **fluoride ions within Enflurane cause hepatotoxicity** so it is not used anymore.

3- Isoflurane (most commonly used) : it is safe on the liver and does not produce cardiac arrhythmia however **it produces a dose dependant hypotension** so if we control the dose we will not produce hypotension .

Note: one of the disadvantages of isoflurane are that it causes irritation of the respiratory tract and this irritation is really dangerous in patients with **asthma or COPD** so in those patients we switch to halothane instead of isoflurane for the maintenance of anesthesia (IMPORTANT)

4- Nitrous oxide (N2O): its commonly called the laughing gas, it is a very important drug because it help to induce analgesia rather than anesthesia in the patient that's why this gas is frequently employed in a percentage of 30% in the anesthetic machine. (remember that nitrous oxide alone will never induce unconsciousness)

Note: the anesthetic machine is composed of three pipes for oxygen, halogenated hydrocarbon (Isoflurane) and Nitrous oxide each one of them in a pipe .

Why do we have a high percentage of Nitrous oxide employed in the anesthetic machine?

1- Because of its analgesic activity
2- It produces an effect called **second gas effect** (IMPORTANT)

What is second gas effect?

Since nitrous oxide once inhaled leaves the alveoli very rapidly into the blood it creates a negative pressure inside the alveoli that allows more of the anesthetic (isoflurane) to be inhaled from the anesthetic machine , this makes the concentration of isoflurane in the alveoli high which creates a concentration gradient that pushes it toward the blood as if nitrous oxide gets out of the alveoli as sucks isoflurane along with it ,this is called second gas effect .

-Nitrous oxide is frequently employed in dental procedures since it causes **sedation** (sedative anesthesia) , **hypnosis** and **analgesic activity** but it will never induce unconsciousness so the patient will respond to external stimuli .

Disadvantages of nitrous oxide :

The main disadvantage of nitrous oxide is that it causes something called **diffusion hypoxia** which happens once we remove the mask .what is the mechanism of diffusion hypoxia?

Since Nitrous oxide rapidly enters into the blood it also will rapidly leave the blood once we remove the mask so it builds up and occupies the alveoli leaving no space for oxygen to enter so the patient will have troubles in breathing for a few minutes after we remove mask, This is rare but can happen (-_-) .

Advantages of nitrous oxide

Analgesia , sedation and hypnosis as we said before and has moderate to no effect on the heart and it's the least hepatotoxic out of all the anesthetic agents .

IntraVenous Anesthesia

- Intravenous anesthetics are used to **INDUCE** anesthesia.

- After that we maintain the anesthesia with a proper inhaled agent.

Q. Why not to use an inhalation anesthetic agent to "induce" anesthesia?
Because it takes long time.

Now we are going to talk about three IV drugs: Barbiturates, Propofol & Ketamine.

1. Barbiturates:

- Thiopental has been used to induce anesthesia for long time, but now it's not the drug of choice anymore since it was linked to many problems and side effects such as:
  - It produces hangover for relatively long period (36 hours).
  - May produce respiratory depression.
  - After certain concentration it turns from first order kinetics to zero order kinetics, resulting in buildup of the drug in the body.
  - Other side effects: coughing, chest wall spasm, and bronchospasm.

2. Propofol:

- Commonly called "the milk".
- Considered the drug of choice to induce anesthesia nowadays, almost used in all cases (actually, some hospitals are still using thiopental because it's cheaper).
- From slides: propofol has replaced thiopental as the first choice for anesthesia induction and sedation, because it produces euphoric feeling in the patient and does not cause postanesthetic nausea, vomiting & hangover.
- Mechanism of action: potentiation of GABA.

- May produce hypotension (but not very profound).
- Reduces cerebral blood flow (advantage).
- Propofol is available as emulsions only, this has two disadvantages;
  a. it's painful to inject the drug.
  b. once opened, this environment promotes growth of bacteria, hence short shelf life of open solution.

3. Ketamine:

- A short acting, induced anesthetic.
- Induces a "dissociated state" in which the patient is unconscious but appears to be awake and does not feel pain, so it's sometimes called the **dissociation drug**.
- Provides sedation, amnesia & immobility.
- Stimulates the central sympathetic outflow, which causes stimulation of the heart and increased blood pressure, and cardiac output. This has two applications:
  - never use ketamine with hypertension or stroke patients.
  - ketamine is used in patients with either hypovolemic or cardiogenic shock, as well as in patients with asthma, this feature can be beneficial to them.
- Ketamine is not widely used because it increases cerebral blood flow, and induces postoperative hallucination particularly in adults.
- it is mainly used in children and young adults for short procedure (doctor says he don't believe it's really used).
- Some people abuse this drug, they use it to "dissociate" from life.

Local anasthetics

- Drugs: lidocaine, procaine, tetracaine … (any drug with the suffix –caine)
- All local anasthetics contain three structural components: an aromatic ring, a connecting group (either ester or amide) & an amino group.

- Local anasthetics are classified into either ester or amide local anesthetics depending on the connecting group. The ester local anesthetics produce more allergy than the amide ones.
- Mechanism of action: block the initiation and spread of action potential in nerve fibres by blocking the voltage-gated Na^+-channels (remember: Na^+ is important in both initiation & propagation of action potential).
- The first sensation that will be lost is pain sensation, but the motor pathways won't be affected relatively, why?
  Pain is transmitted by slow fibers, and Na^+-channels remain open relatively for long period giving high chance for the drug to block the channel. On the other hand, motor commands are transmitted via fast fibers where Na^+-channels open and close rapidly giving the drug less chance to block them.

- So the patient firstly loses sensation of pain, then temperature, then sympathetic activation and then finally he MAY lose his motor activities. (He will only lose motor pathway if he is given a very high dose that may even be toxic).

Chemistry of Local Anesthetics:

Remember the Henderson-Hasselbach equation: pH=pKa + log base/salt
This allows us to determine the ratio of ionized to unionized drug in a solution.
All local anesthetics have an amino group. All amino groups have the potential of taking up an H+ and becoming ionized. NH3 + H+ ----> NH4+

This all depends on the pKa. If the pH of the solution equaled the solution's pKa, then there is an equal proportion of ionized to unionized compound.
All local anesthetics are weak bases, with pKa's around 8- 9 (closer to 9). When we inject these local anesthetics into the patient, it will be put in a more physiological pH (the ph of the body, = 7.4). The local anesthetic will undergo ionization.
Why is this important?

The more unionized the local anesthetic drug is, the more lipophilic its structure will be, and the more easily it will pass through the nerve membrane. It must cross the nerve membrane to be active.
If it is ionized, it cannot cross the membrane, and will not exert its activity.

Example: Calculate the proportions of free base and salt forms of tetracaine (pK = 8.5) at pH (7.5). **pH=pK + log [base]/[salt]**

7.5 = 8.5 + log [base]/[salt]
log [base]/[salt] = -1

[base]/[salt] = 10^{-1} = 1/10

So the proportion of the unionized drug (base) to ionized (salt) ends up as 0.1.
And so, only a tenth of the drug will be able to cross the nerve membrane.

If there was inflammation, the pH will drop and become acidic. When the pH becomes acidic, the difference between the pH and pKa will become greater (in the example above, instead of being -1 it might be -2). Subsequently, a much smaller proportion of the drug will be unionized and cross the nerve membrane.
This has clinical importance when dealing with inflamed areas. In these areas, the dose of the anesthetic must be higher.
{The more acidic the environment, the less unionized local anesthetic will be available in the

environment}

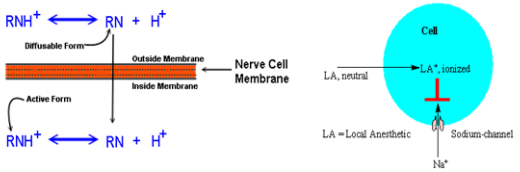
The drug has to cross the membrane, and to do so it must be unionized.

Very simple words.

Sometimes, the doctor will add Bicarbonate (H2CO3) to the solution before injecting. Why?

To increase the pH of the solution, and this will increase the amount of unionized drug, increasing its penetration.

local anesthetic **enters** nerve fibre as **neutral free base** and the **cationic form blocks conduction** by interacting at inner surface of the Na^+ channel



inflammation → **reduced** susceptibility to anesthesia (lowered local pH increases proportion of anesthetic in charged form that cannot permeate nerve membrane

Functional consequences of Na^+ channel blockade by local anesthetics:

1- The nerve will be blocked, Its conductivity will be decreased.

2- Vasodilation of vascular smooth muscle. (blocking of Na+ channels will relax the smooth vascular muscles, leading to vasodilation.) (This is why thiazide drugs have a vasodilatory effect) (wait no this is CNS sorry)

3- Several effects on the heart like; decreased excitability (reduced pacemaker activity, prolongation of effective refractory period).

4- **CNS; increased excitability, followed by generalized depression.**

These are bad unwanted side effects (numbers 2,3, and 4). Imagine injecting Lidocaine into an area, and along with the already diffusing substance we have the effect of vasodilation. This will make the Lidocaine spread out further than our intended area of action.

You've definitely taken with Dr. Yaqoub that we must add a vasoconstrictor with the local anesthetic. We always use the vasoconstrictor adrenaline. So adrenaline is used to decrease the diffusion of the local anesthetic away from the local intended area of anesthesia. Adrenaline is also used to decrease the other unwanted side effects of the local anesthetic. We add a very low amount (1/100,000), but this very low amount will (1)

keep the drug within the area of interest and (2) will reduce the side effects. The most toxic route of administration is IV, so adding a vasoconstrictor will slow down the diffusion and lower the peak of the drug.

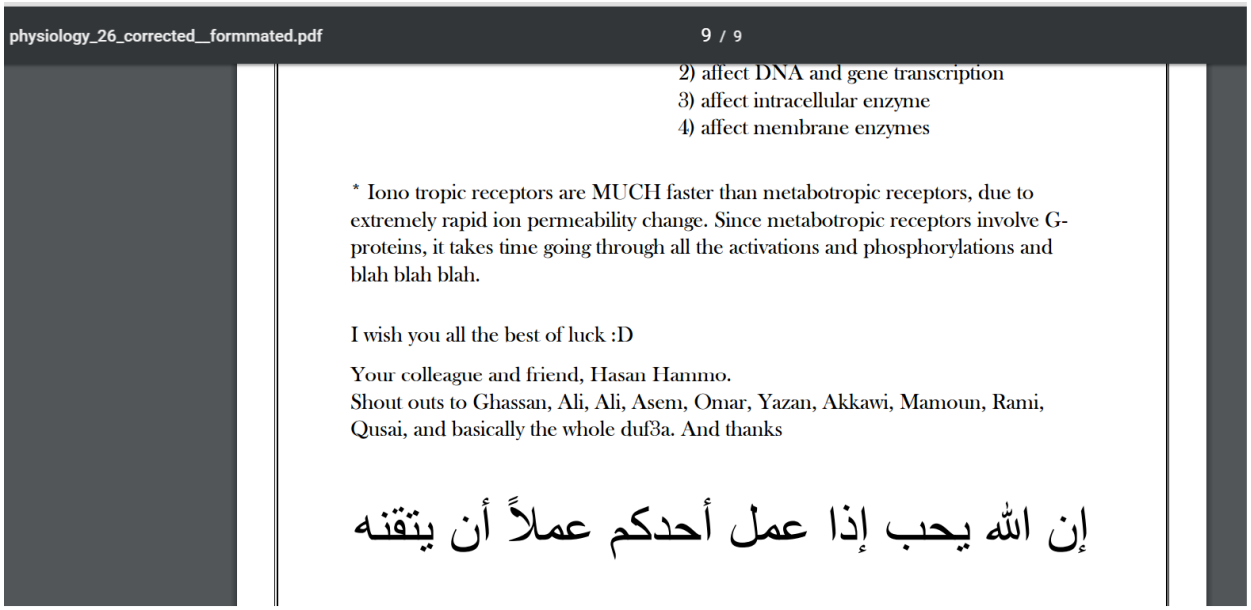
Keeping the drug in the area of interest prolongs its life there and extends its usability by increasing its concentration in that area and reducing the chance of side effects.

In conclusion

1- Anesthetics are weak bases, and pH of the area where you inject the drug is very important. It plays a major role in the amount of unionized local anesthesia, so dose the patient differentially according to his health status (ex. IFM) .

2- Local anesthetics are toxic drugs, so we add vasoconstrictor to prolong their action and to reduce unwanted side effects.

Uses of local anesthetics include: Dental, topical use on skin, and spinal and epidural. (Next lecture)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2) affect DNA and gene transcription
3) affect intracellular enzyme
4) affect membrane enzymes

* Iono tropic receptors are MUCH faster than metabotropic receptors, due to extremely rapid ion permeability change. Since metabotropic receptors involve G-proteins, it takes time going through all the activations and phosphorylations and blah blah blah.

I wish you all the best of luck :D

Your colleague and friend, Hasan Hammo.
Shout outs to Ghassan, Ali, Ali, Asem, Omar, Yazan, Akkawi, Mamoun, Rami, Qusai, and basically the whole duf3a. And thanks

إن الله يحب إذا عمل أحدكم عملاً أن يتقنه

That's the end of this lecture, and I hope it wasn't too hard.

This sheet is dedicated to Khaled Smadi, Ali Khresat and Ali Tamimi, our saviors.

Also can't forget Mr. 6.5

These are the last days of our basic years inshallah, so study hard and don't loosen up one bit. Do what you have to do and perfect it.

I wish you all the best of luck :D Good times :')

Your colleague and friend, Hasan Hammo.