CENTRAL NERVOUS SYSTEM

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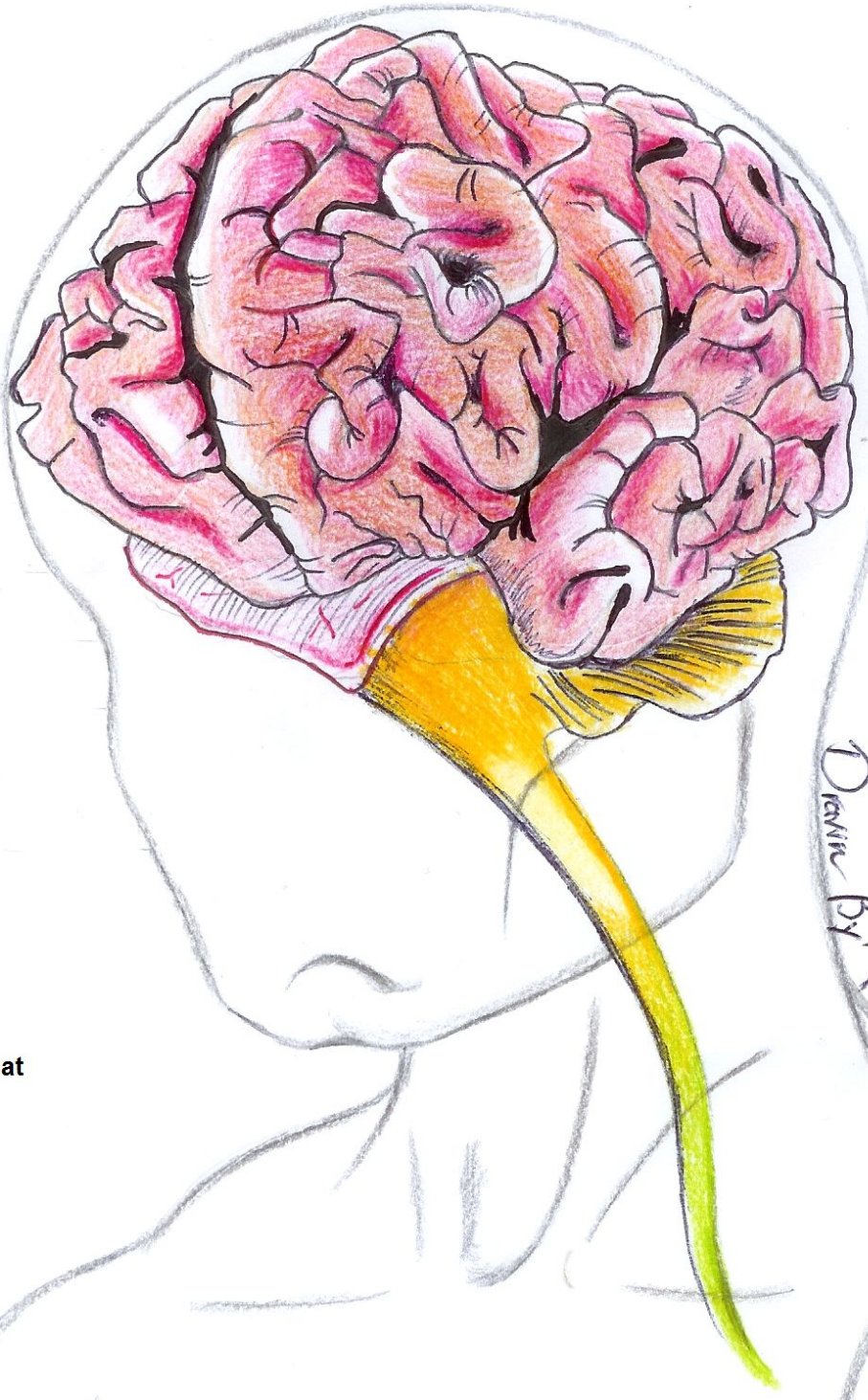

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Opioids

Introduction

-Pain in general has degrees ranging from mild-moderate-sever pain. Each degree of pain generally respond better to certain analgesics than others.

- We took last year in the musculoskeletal system pharmacology about NSAID and we said that there are certain NSAID like profen, naproxen, diclofenac, celebrex that work as analgesics for the treatment of **mild to moderate pain** however if a patient come to you with severe pain and you gave him these drugs it would be as you have dosed him with nothing because they will do nothing for his pain, Why?

This is related to a concept called **ceiling effect** in which a drug reaches a maximum analgesic affect and analgesia does not improve even if you increase the dose . in the case of NSAID the maximum analgesic effect is for moderate pain and have no effect on sever pain .

-Conditions associated with severe pain include:

1. Terminal stage cancer pain
2. Post-operative pain after a major surgery like cardiac bypass surgery
3. Labor pain
4. Bone fracture pain

-In these conditions of severe pain we use drugs called Opioids or narcotics. As always the doctor said that these are the best magical drugs introduced in pain management pharmacology however they are associated with the nightmare of ADDICTION and MISUSE worldwide.

-You might think that post-operative pain can be managed with anesthesia (local or general) however you MUST supplement anesthesia with opioids so you are going to use these drugs a lot in your career.

-Opioids include the following drugs : Morphine , tremadole , codeine , oxycodone and heroin.

Pharmacodynamics of Opioids

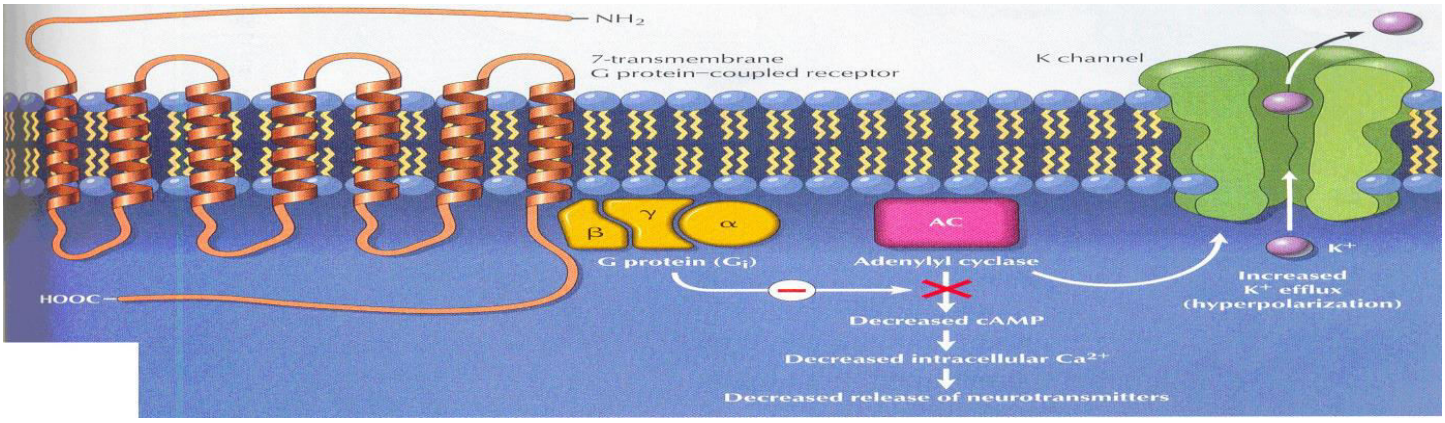
-Opioids act by binding to opioid receptors which are found in both CNS and PNS. Endogenous analgesic ligands called Endorphins and Enkephalins -which are produced inside our body- bind to opioids receptors, when Opioids bind to these receptors they augment (enhance) the action of endorphins and enkephalins and produce analgesia.

- Opioids receptors are of three types:

1. Mu (μ) receptors : the most common receptors that Opioids, enkephalins and endorphins act on
2. Kappa receptors
3. Delta receptors

-What happens when Opioids or endorphins bind to Mu receptors? They will induce 2 major events:

1. They activate Mu receptor which is G-protein linked receptor and the type of G protein is **inhibitory** (Gi) which inhibit adenylyl cyclase therefore decreasing the level of cAMP inside the cell and this will inhibit the transmission of the message.
2. They open K+ channel decreasing K+ concentration inside the cell causing a state of **hyperpolyrization**.



- The net effect of these events decrease neuronal excitability due to hyperpolyrization therefore inhibiting the transmission of pain from receptors to higher centers.

- Because Opioids decrease level of cAMP inside the cell this will decrease Ca++ influx in GI tract cells causing CONSTIPATION which is the most common side effect when using Opioids.

Indications for using Opioids

1- Moderate to severe pain

- We use them in moderate to severe pain because other analgesics which are non-addictive like NSAID won't work.

2- Dry or none productive cough

- Generally in these conditions we use **codeine or dextromethorphan** which are both Opioids with the ability to suppress **cough centers in the brain** exerting an **antitussive** effect

Remember that you should be very careful when using these antitussive drugs in children since any increase in the dose can inhibit the respiratory centers which are found near the cough centers causing respiratory depression and death .

3- Diarrhea

- As we said Opioid receptors (Mu ,delta , kappa) are found in CNS and also peripherally one of these peripheral sites is in the GI tracts (stomach, small and large intestines), when these receptors get activated this will decrease level of cAMP in the GI tract cell followed by a decrease in Ca++ influx eventually decreasing peristaltic contractions of the GI tract which can treat diarrhea .

- You can say here that we used the side effect of Opioids which is constipation to treat diarrhea.

4- Balanced Anesthesia

- It's a procedure in which we mix anesthetics with Opioids in order to decrease the dose of anesthesia which in order decreases the mortality rate.

Opioid side effects

1- CNS depression

Because they induce a state of hyperpolyrization which decrease neuronal excitability

2- Nausea and Vomiting

This is caused by the binding of Opioids to the vomiting and nausea centers in the brain stem causing vomiting and nausea so they activate these centers.

3- Respiratory depression

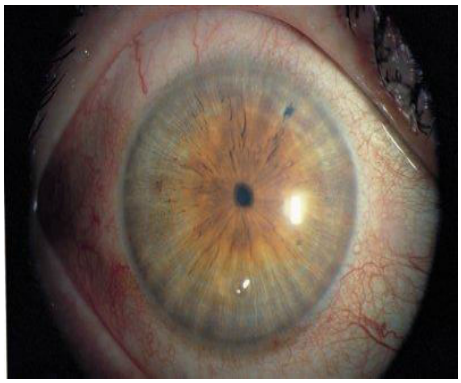
This is the most serious side effect and it's the third most common cause of death in the US in people addicted to Opioids. CO_2 levels within blood will increase without detection by respiratory centers.

4- Urinary retention

The mechanism is similar to some extent to constipation.

5- Diaphoresis and flushing

6- Pupil constriction (miosis)



This is a very important side effect that lasts for a long time after the use of Opioids, the appearance of the pupil is called **pinpoint pupil**.

Writers note: if you suspect that a person is addicted to Opioids the most prominent sign that can help you to confirm this is the appearance of the pupil.

7- Constipation

8- Itching : related to the release of **histamine.**

9- Euphoria

It's a mental and emotional condition in which a patient experiences an intense feeling of well-being and happiness which is induced by **activating the reward centers of the brain,** Opioids stimulate the release of **dopamine** by an unknown mechanism and this dopamine is the main activator of the reward system giving the patient euphoria. This side effect is the main cause of addiction to Opioids.

Tolerance, dependence and addiction

These are the main problems associated with Opioids administration and we are going to explain each one of them in details and you must be able to differentiate between them.

- Tolerance: we have already talked about it in the introductory course and we said that tolerance develops when you dose your patients with an agonist for a prolonged period of time the body will respond by down regulating the number of receptors therefore the dose of the drug that used to produce a pharmacological effect will not produce the same effect the next time.

In order to understand mechanism of tolerance in relation to Opioids you must understand a concept called **receptor recycling** in which Opioid receptors (Mu receptors for example) get activated by endogenous material like endorphins then the receptors get endocytosed inside the cytoplasm, reactivated and then come back to the surface of the cell so it can bind new endorphins over and over again this is what normally happen to those receptors. **However if a patient used morphine drug which is exogenous in an excessive way the cell will choose to degrade those endocytosed receptors instead of recycling them decreasing the number of receptors on the surface. When you give the drug the next time, it'll not find much receptors to bind to.**

-Tolerance is really a problematic issue when dealing with people addicted to Opioids because these people look for **euphoria** however the dose of the drug that gave them euphoria in the first week will not be effective in the second week **so they will keep increasing the dose until they end up with respiratory depression and be found dead in the streets.**

- The problem of tolerance is also important in our clinical life because we need to suppress the patient's pain, how it can be managed? **By gradually increasing the dose in simple quantities** until reaching the maximum limit at which any increase in the dose will produce respiratory depression.

Important note : tolerance develops against the analgesic effect of Opioids and all their side effects EXCEPT **pupil constriction and constipation** , there is no tolerance against these two side effects because the pupil and GI tract are outside the CNS and have a low number of Mu receptors already so tolerance can't happen in this case .

- Dependence : **it is a physiological phenomenon in which continuous intake of exogenous material depress the production of endogenous material** .if you continuously dose your patient with morphine the body will say why the hell should I synthesize enkephalins and endorphins therefore the body stop producing them , **this is independent of tolerance**.

What will happen if a patient suddenly stopped taking morphine? The patient will end up with a syndrome called **Abstinence syndrome** which is characterized by a group of symptoms collectively called **withdrawal symptoms (these symptoms are opposite to the effect of morphine).** In order to prevent this syndrome from happening we need to gradually decrease the dose then stop the drug.

If you remember this condition is very similar to withdrawal issue associated with cortisol treatment in which continuous intake of cortisol causes the adrenal gland to become atrophic and when you suddenly stop the intake of cortisol the body will not have cortisol to compensate for that so the patient will end up with **adrenal insufficiency**.

Withdrawal reaction (the opposite of the acute reaction of the drug)

Acute reaction	Withdrawal reaction
Analgesia	Pain and irritability
Respiratory depression	Hyperventilation
Euphoria	Depression
Relaxation and sleep	Restlessness and insomnia
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupillary constriction	**Pupillary dilation**
Hypothermia	Hyperthermia
Tranquilization	Fearfulness
Drying of secretions	Lacrimation, runny nose
Flushed and warm skin	Chilliness and "gooseflesh"

These withdrawal reactions are helpful to diagnose if your addicted patient for example has really stopped taking the drug.

- **Addiction:** Psychological & behavioral syndrome manifested by drug seeking behavior, loss of control of drug use, and continued use despite adverse effects.

Keep in mind that addiction is completely different from tolerance and dependence simply because the idea of addiction comes from a psychological aspect which is "I cannot live without the drug." that is usually encountered with street users who used these drugs in the first place to get rid of their problems and feel euphoric.

This condition is very similar to smoking because smokers think that they need to smoke whenever they are angry or after they eat or whatever and this is actually a psychiatric issue.

Note: what do we mean by free intervals? To give the patient a drug for 16 hours for example and stop it for 8 hours. For opioids, we have opioids holidays, it means to stop opioids therapy for 2-7 days, this is important for regeneration of the receptors (to re-sensitize the body toward opioids).

Drugs used as Opioids

- Opioids are divided according to their analgesic activity into weak Opioids and strong Opioids.

Weak Opioids	Strong Opioids
Codeine	Morphine
Tramadol	Oxycodone
	Methadone
	Fentanyl
	Mepiridine

- The doctor is going to talk about each one of them in details in next coming lectures

Morphine

- It is the first drug that is introduced to the market as an Opioid, it's mainly used in **analgesia.** It's not used an anti-tussive.
- The main differences between morphine and other strong Opioids (Oxycodone, methadone …. Etc) are:

1- It has the highest euphoric activity. (Important)
2- It was used for the treatment of acute pulmonary edema linked with congestive heart failure while other drugs were not effective.

- The mechanism behind using morphine in the treatment of acute pulmonary edema is not known however there are many theories that explains this one of them said that when a patient uses morphine his stress level is going to be reduced and this reduces the level of pulmonary edema (Obviously this is still not well understood) .

- Keep in mind that nowadays the main drug used for the treatment of acute pulmonary edema is **furosemide** (lazix) and morphine is not used anymore.

- The doctor read the following about morphine from slides:

Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, morphine may be used to supplement the sleep-inducing properties of hypnotic agents.

Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscles.

Morphine produces a powerful sense of euphoria and wellbeing.

Morphine is also used in the treatment of acute pulmonary edema, intravenous morphine is dramatically relieve dyspnea cause by pulmonary edema associated with left ventricular failure.

End of this sheet

Special dedication to Muhannad Haddadin for correcting this sheet.