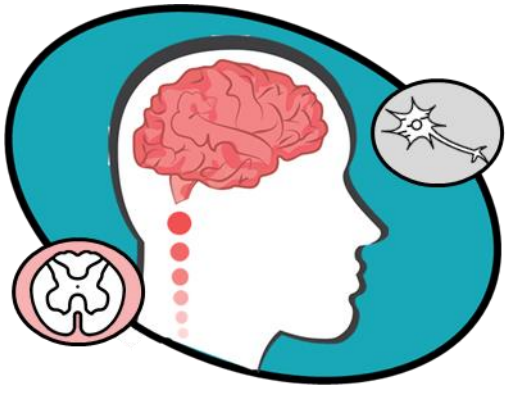

CNS

Physiology

Sheet Slide

Number

- 13

Done by:

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- **Today we are going to talk about these concept:**

- Pain pathways
- Descending pain control
- Opoid neurotransmitters
- Non traditional neurotransmitter
- Introduction about cerebellum

- **Pain sensation :** pain sensation starts from the receptors (free nerve ending) at periphery of the body then these 1rd order neurons that transmit pain sensation will synapse at dorsal horn of spinal cord especially lamina 1, 2 and 5 then 2nd order neurons will cross to the contralteral side of spinal segment and ascend forming **anteriolateral spinothalamic tract** (ALS) that ends in the **thalamus** and then 3rd order neurons of thalamus will go to the **cortex** specifically to the primary somatosensory cortex (area 3,1,2) .
  - ➔ This pathway is the primary pathway of pain sensation and it is called " **Neospinothalamic pathway** " This pathway is responsible about **conscious part of pain sensation** because it ends at the cortex. Also, it is responsible about sensation of sharp well localized pain because the neuronal fibers of this pathway are considered **fast fibers**.
  - ➔ The other pathway of pain sensation is called **" Paleospinothalamic "** pathway responsible about **unconscious part of pain sensation** because the 2nd order neurons will enter multi synapses at different stations other than entering in the thalamus and cortex but remember these subcortical areas are always under the control of cortex. **Paleospinothalamic pathway contains :**
  - ➔ **Spinomesencephalic pathway :** Here 2nd order neuron will synapse at **Periaquedactal gray** which is a gray matter that found around cerebral aqueduct in the midbrain. Periaquedactal gray is responsible about **processing of pain and pain control** (we will talk about

this in the next section of this sheet). This gray matter contains descending autonomic neurons so it has **a relationship with ANS .** Also it has **a connection with hypothalamus for regulation of internal environment** and it has a role in **how do you response to sudden stimulus (affected response).** Note: the doctor talked about these functions of periaquedactal gray without mentioning the details of these functions.

➔ **Spinoreticular pathway:** 2nd order neuron goes to the reticular formation activating RAS resulting in decreasing sleeping and this is the cause that you will be awake at night and you can't sleep easily when you have specific pain.

➔ **Spinohypothalamic pathway**

➔ **Spinobulber pathway**

The doctor didn't talk about them

- **Descending control of pain:**

Central Conscious regulation by the cortex: Here the cortex descends fibers to inhibit the spinal cord (spinal cord down regulation) and so inhibition of pain sensation. But these descending fibers from the cortex actually not directly inhibit the spinal cord but they go to the hypothalamus and periaquedactal gray and those will inhibit spinal cord.

➔ **Notice** this is central regulation of pain by cortex resulting in reduction of pain sensation according to your conscious level. for example people that train themselves to move on burning coal will try consciously to suppress pain sensation.

Control by hypothalamus and periaquedactal gray:

Periaquedactal gray matter contain neuronal cell bodies and neuronal axons project from them. neuroproteins are synthesized in neuronal cell bodies unlike non peptide neurotransmitters that synthesized in nerve terminal. So these neuroproteins will be transported as a large vesicles by axonal transmission to the nerve terminals. This transportation will consume alot of energy and so the axon is designed to be short- distance axon to decrease energy consumption. Now, neuropeptides reaches the

nerve terminals and they are ready to be released. When action potential is generated in periaquedactal neurons will result in releasing of these neuroproteins. They will act on postsynaptic neurons in raphe nuclei, the axons projecting from raphe nuclei will synapse by their terminals with inhibitory interneuron in spinal cord. So when neuroproteins act on raphe nuclei , raphe nuclei neurons will release seretonin in the synapse with inhibitory interneurons and activating them. These inhibitory interneurons will inhibit the synapse between 1st order neuron and 2nd order neuron so there will be inhibition to the signal to reach 2nd order neurons and consequently elimination of pain sensation.

Note : there is no direct connection between periaquedactal neurons and spinal cord because that require very long periaquedactal neuron and that will result in consumption alot of energy by axonal transport of neuroprotein. So periaquedactal neurons have short axons to synapse with raphe nuclei and then neurons projecting from raphe nuclei go to spinal cord.

Note: periaquedactal neurons and inhibitory interneurons BOTH release neuroproteins which are from **opoid** family

Control by locus coreulus: Norepinephrine exist in a small area in the brain known as locus coreulus in brainstem, from there **ascending** norepinephrine fibers go to **cortex** especially prefrontal cortex and **descending** norepinephrine fibers go to the **spinal cord**. **Ascending** fibers are **excitatory** and **desending** fibers are **inhibitory**. So:

- ➔ Its effect is excitation to cortex and inhibition to spinal cord. When there is a stimulus, locus coreulus will send norepinephrine to cortex, especially the prefrontal cortex, so prefrontal cortex will send orders to focus your attention on this new stimulus and inhibit other stimuli, and when prefrontal decides that this new stimulus is not important, it will send signals to locus

coreulus to send norepinephrine to spinal cord to inhibit this stimulus.

➔ The same thing in pain sensation , descending norepinephrine fibers will inhibit spinal cord.

Note: If the patient has a chronic pain due to cancer or something else, you can prescribe serotonin and norepinephrine because Both are pain relievers and Both considered anti depression drugs that alleviates patient's mood. " عصفورين بحجر"

There is a surgery done to alleviate pain by putting stimulator electrode that stimulate periaquedactal gray continuously resulting in pain relieving.

- **Opoids neurotransmitters:** they are neuropeptides that their main function is decreasing suffering and pain . Remember when we said that the main neuropeptides released from periaquedactal gray and inhibitory interneurons are Opioids!. **We will talk about three groups of opiods that are divided according to the receptors they act on:**
  1.Enkephalin(delta receptor).
  2.Endorphine(mu receptor).
  3.Dynorphin(kappa receptor) → they are not well distributed in CNS so we will not talk about them

➔ **Enkaphalin:** found in **neurons of periaqueductal grey and acts on delta receptors on raphe neurons.** Also **it is found in inhibitory interneurons of spinal cord and acts on delta receptors on the synapse between 1st and 2nd order neurons** resulting in its inhibition. However, the most dominant receptors on the spinal cord at the level of this synapse are mu receptors so enkaphalin result in slightly inhibition of pain. This is the reason why in

clinical practice we give endorphine rather than enkaphalins because they act on mu receptors (the dominant one) resulting in more pain inhibition.

➔ **Endorphins:** most commonly found in CNS and its receptors (mu receptors) are distributed in many areas in CNS. They are similar to morphine which is mu receptor agonist. They are also well presented in **cortex** so endorphin can **inhibit conscious pain**. They also present in all centers in **brainstem** and because of that they are able to **decrease perception of pain in thalamus**, **emotional stress of pain in midbrain and hypothalamus**. But the problem here is that its effect on brainstem is inhibitory, so a high dose of it will inhibit respiratory center in brainstem and there will be respiratory arrest. Also at higher dose, it can stimulate nucleus accumbens and result in euphoria but this does not usually happen because the main action of endorphins is inhibitory. Endorphins also result in **inhibition of hypothalamus** function so the result is **decreasing body temperature regulation and endocrine functions.** Brain stem contain **unconscious centers of internal reflexes (cough and gas reflex " vomiting")** we can use endorphins to inhibit these reflexes**.**

- **Non traditional neurotransmitters:** we will talk about one of them which is **B**rain **D**erived **N**eurotrophic **F**actor " **BDNF**"

➔ It is a neuroprotein that can act as other normal neuroproteins in which it is synthesized in neuronal cell body and then being transported to axon terminals and then released to act on Tyrosine kinase receptors of postsynsptic neuron (2^{nd} messenger receptor). The result is increasing growth, division ,cell proliferation and activating plasticity pathway. So the main function is **cell survival and growth.**

➔ **However, BDNF is non traditional neurotransmitter** because in many neurons BDNF found in vesicles of cell body and dendrites without going to nerve terminal. So they being released from postsynaptic neuron toward synaptic cleft and they will act on presynaptic neuron. This is called **Reverse action .**

➔ **Note:** Releasing of BDNF from cell bodies and dendrites needs also Ca++ so any neurotransmitter from presynaptic neuron that result in opening calcium channel on the postsynaptic neuron will result in releasing BDNF from presynaptic neuron toward postsynaptic neuron.

➔ Remember : we studied before that glutamate neurotransmitter act on NMDA receptors resulting in influx of Ca++ in the postsynaptic neuron.

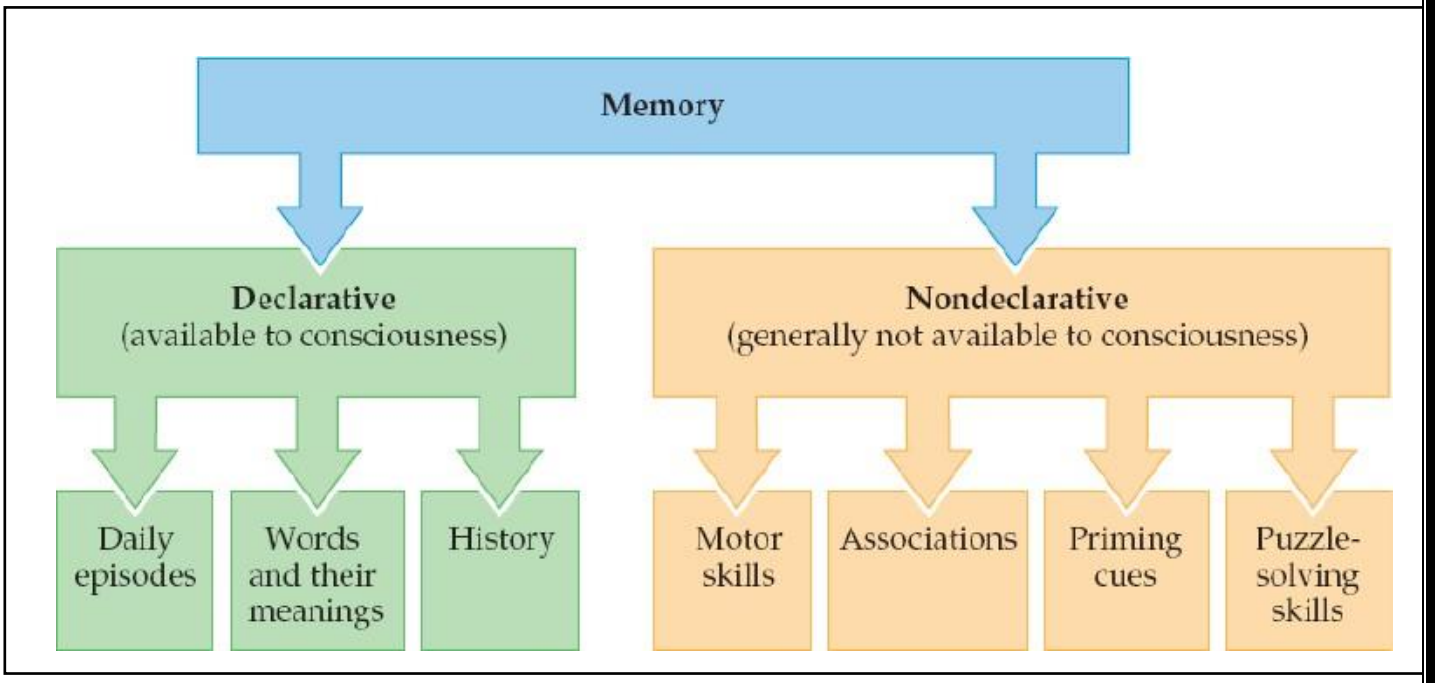
➔ So we conclude that postsynaptic neurons that contain BDNF in cell body" should have mainly NMDA receptor and the presynaptic neuron should release glutamate.

➔ Other neurotransmitters leads to influx of ca++ are seretonin, norepiniphrine but the main one those acting on NMDA receptors.

Note the synapses that contain BDNF will servive for longer time than the synapses that doesn't contain BDNF

➔ BDNF is important for **memory** and **plasticity** of brain.

- Memory: we have **two** types of memory;**Declarative** memory and **non-declarative** memory
  - ➔ **Declarative (general facts)** : conscious part of memory which means early memory in which it involves answers to direct questions like (what's your name). This memory iis on the level of cortex
  - ➔ **Non declarative :** Unconscious part of memory which involves skills , making association between informations and classical conditioning. This memory is on the level of subcortical areas especially cerebellum.



- Memory also is divided according to **time** into:
  - ➔ Short term memory : which represents recent activations to group of neurons or there is reverberating circuit that cause continuous activation to these neurons.
  - ➔ Long term memory: this memory can last for days, weeks and even years due **anatomical** and **physiological** changes of series of neurons that makes their activation easier.

- **Physiological changes**: It Includes physiological coupling between neurons in which action potential of presynaptic neuron will ALWAYS for sure result in action potential on postsynaptic neuron (which means that the action potential of presynaptic neurons will ALWAYS result in high number of graded potentials on postsynaptic neuron that ALWAYS result in action potential). This is called **long term potentiation.**
  How?
- **Remember again** BDNF needs Ca++ to be released and this occurs due to seretonin, norepinephrine action. But as we said

the most prominent one is NMDA receptor and its neurotransmitter glutamate. **Notice** that as we took that NMDA needs continuous activation by glutamate to result in calcium influx and this is actually happen in Rem sleep in which the cortex is turned on and it will cause continuous activation to NMDA receptors and this process called **reconsolidation**. So notice the relationship between rem sleep and long term memory.

By Anatomical changes : the number of synapses between presynaptic neuron and postsynaptic neuron is higher due to many causes :

- ➔ **Presynaptic Neuron axon makes higher number of axon terminals.** (Higher number of synapses)
- ➔ **Or Axon terminal synapses at peripheral part of dendrites at closer location to axon hillock** (increase the possibility of generation action potential)
    - **Notice** that the presynaptic axon will become bigger and the number of terminals is higher so the number of synapses is higher. Notice also spines which represents the anatomical location of synapse will become higher in number and more prominent (These spines represents anatomically as small dots or buds on cell body and dendrites of postsynaptic neuron). Theses changes actually need BDNF which represents the **chemical change** that accompanies long term potentiation process.

- **Introduction to cerebellum**

Cerebellum is one of subcortical areas. It has many roles and the most important role is motor regulation. It is also a regulator to the cortex and the best way to describe its function by calling it statutory auditor of all parts of CNS . For example, it audits the motor order descending from cortex to make sure that you achieved your motor intention so when you want to throw something to another person and if you didn't achieve your goal in the first time, at the second time the cerebellum will adjusts and edits the motor order to achieve your goal by calculating the distance, the strength of motor movement, etc. When you try many times to achieve your goal, cerebellum is still doing its caculation and when you achieve your goal it will save these calculations so next time you will achieve your goal easier.

A very easy example to understand the cerebellar function in motor regulation is trying to teach a child how to hold an egg,when the child tries to hold the egg he will either use too much pressure breaking the egg or too little dropping it. What happens is that the cortex gives a motor output“X” and when the child holds the egg too hard breaking it the sensation he will get is that he used too much effort and here the cerebellum makes an adjustment that we need to reduce the motor output to“1\2X or 3\4X…etc” to hold the egg with outbreaking it,the child tries again and this time he drops it so the cerebellum makes another adjustment increasing the motor output,he tries athird time breaking It so the cerebellum reduces the motor output again and this goes on and on until finally the child learns the exact amount of pressure needed to hold the egg and the cerebellum records this amount so the next time the child tries he succeeds**.**

➔ **We conclude** that cerebellum is responsible about coordination between sensation and motor orders.

➔ **So a lesion in cerebellum will result in ATAXIA**