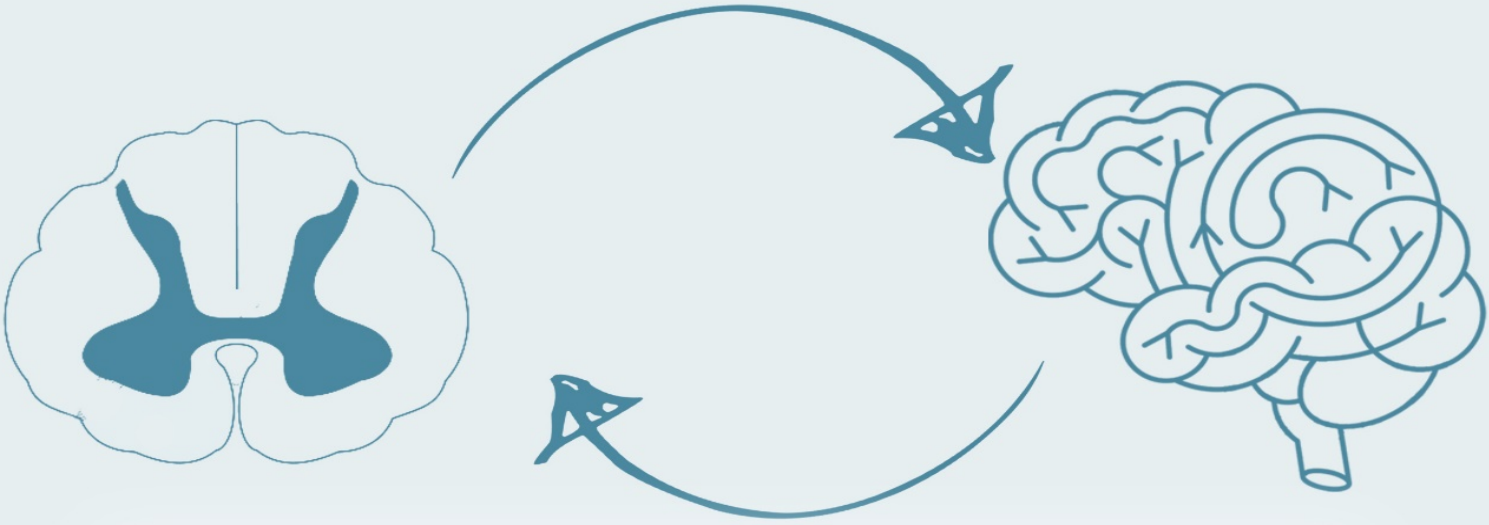


CNS

physiology

slides | sheets

number	21
Done by	Renad zakaria
Correction	GHufran Touma
Doctor	Loai Alzgoul

Non-traditional Neurotransmitters

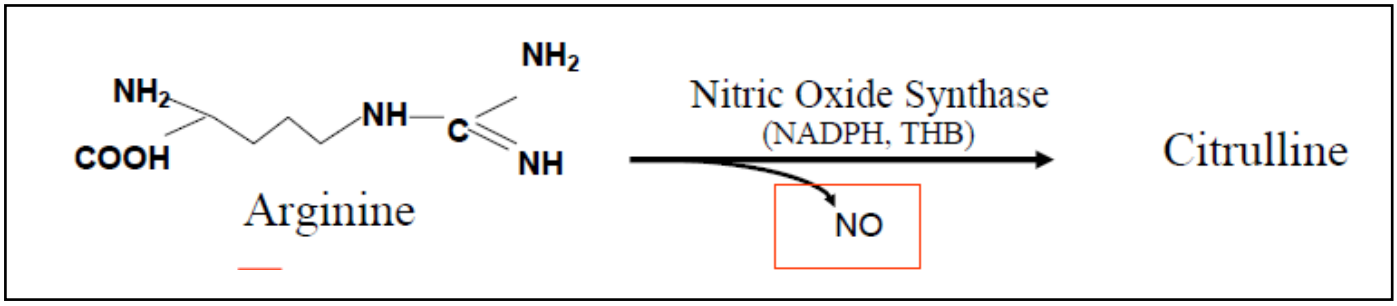
Nitric Oxide (NO)

Nitric oxide is a gas so you can't pack it in a vesicle because it will diffuse directly. So, it must be synthesized upon request and the body needs.

- The cells that produce NO contain NO synthase enzyme, so how it produces NO?

At first action potential will reach these cells, Ca will enter the cells activating NO synthase. Then this enzyme will produce NO that will *diffuse* directly to the neighboring cells reaching the synapse, next→ NO will bind its receptor. NO receptors in turn will increase the entry & the amount of Ca. SO action potential and binding of NO to its receptor will increase Ca so more synthesis and production of NO, it's all related to Ca!!

- The figure below shows the formation of NO:



- As we said NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase, is not stored and synthesis is regulated by the enzyme activity and it's Constitutive Neuronal Ca++ -dependent.

- NO is widely distributed in brain and peripheral tissues.

- NO is get activated by Ca. there is another neurotransmitter that has also a relation with Ca which is **Glutamate and its receptor NMDA** so, this neurotransmitter will activate and has an influence on Nitric Oxide and the neurons that get activated by NO.

Accordingly if the NMDA gets over activating (excitotoxicity), NO will have produced → diffuse to the neighboring cells →bind and activate NO receptors →increasing the level of Ca that may reach its highest level if the NO retain very active leading to →the death of these cells(through apoptosis, sheet19).

All of this describe the death of *non-glutamate neuronal* cells although they don't have Glutamate or NMDA and death of *cells that caused by small ischemia*.

** But what is the relation between stroke (ischemia) and NO?

Just remember what we described and let's explain it as the following:

If we have ischemia >>this will kill neurons by cytotoxicity [glutamate bound to its receptors >>***induce calcium***>> >>drive cell toward apoptosis], and all the neurons in that area will die even the ones that don't have glutamate receptors and the activity of NOS and the deficit might be increased, Why!? Let's repeat it on more time

Neurons has NMDA R , it is overactive and opened in stroke →increase Ca+ → then at a certain level Ca+ activate NO synthase → produce and diffuse NO in high amount → it will go to neighboring neurons (even if it wasn't ischemic) → increase calcium there and eventually drive cells toward apoptosis.

Function of NO

- Regulation of blood flow - Neuron-derived NO plays a major role in the regulation of blood flow, vasodilation and increased blood flow.

- At the cellular level, NO can change intracellular metabolic functions that modify neuronal excitability and influence neurotransmitter release.

- In the brain, NO acts as a neuromodulator to control behavioral activity, influence memory formation, and intensify responses to painful stimuli

- May be responsible for glutamate induced neurotoxicity.

- ***It has a role in stroke and memory (the memory part will be described later).***

Brain-derived neurotrophic factor "BDNF"

- Another nontraditional neurotransmitter, you know that neuropeptide is a protein that acts as neurotransmitter. one of these neuropeptides is the growth factor family that act as growth factor and neurotransmitter, BDNF is one of them.

- BDNF mainly acts through 2nd messenger which is tyrosine kinase receptor.

** Tyrosine kinase receptor act by phosphorylation, its main effect on the cells is cell survival, growth and division.

** But why we call it nontraditional neurotransmitter?

It's the same as the other neuropeptide produced in the nucleus then it transmitted and transported to the axon terminals where it released from there then it goes to postsynaptic receptors and activate them but this describe how it similar to the traditional transmitter!!, we have some areas in the brain where it produced in the nucleus but instead of going to the axon terminals it remains packed in the cell body & dendrites and when an action potential reach them, the cell body & dendrites will be activated and release BDNF from cell body to the axon terminals and we called this **reverse action,** So it called nontraditional neurotransmitter since it acts through tyrosine kinase and reverse action.

We called it **Reverse action since it starts from postsynaptic to presynaptic (it is secreted from postsynaptic despite it is found on presynaptic), and on the axon terminals there are receptor for the neurotransmitters, so when BDNF released from the cell body it binds to its receptor in the axon terminals then this complex will be packed into a vesicle that will be transported back through the axon to the cell body, and there they will do their function by inducing living and growth. Since they are transported as vesicles **Ca** will cause their releasing.

** Actually, there are numbers of studies confirm that we have BDNF receptors on the axon terminals and they don't act as auto regulators, positive or negative feedback mechanisms. In reality when they get activated, they carried back to the cell body and give the cell survival and growth signals.

☼ Until now we talked about various neurotransmitters that act through Ca let's remember them:

1- NO. 2- Glutamate & NMDA. 3- BDNF. 4- Serotonin in BLC system.

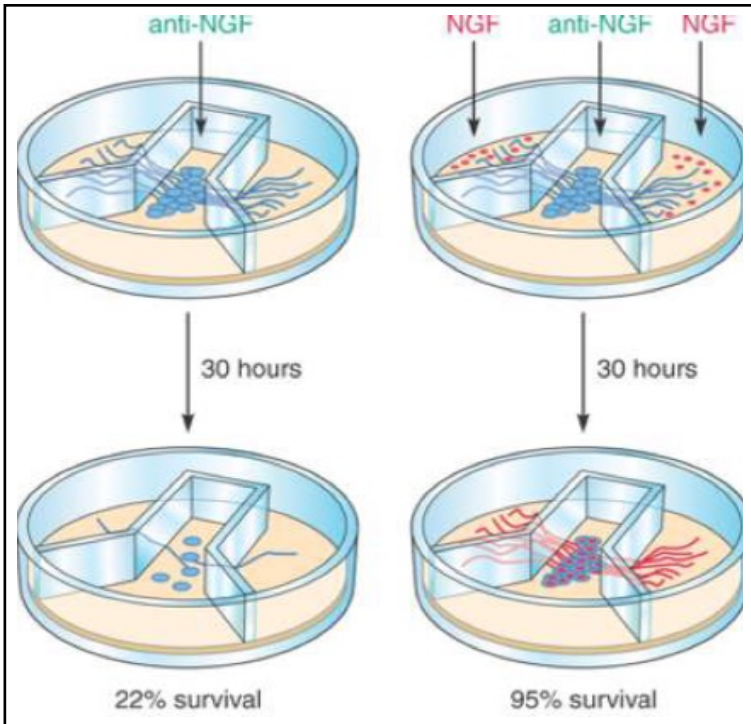
5- Subclasses of norepinephrine.

** As we said there are multiple experiments that study and prove the reverse action, one of the experiments done on this topic is bringing neurons, putting cell bodies in an area/chamber and the axon terminals in another one, then we bring a neuronal growth factor – one of them is BDNF. If we put them in the cell bodies, they will not survive, but if in axons we will detect them in the cell bodies and they induce survival.

- Let's explain this experiment more in details (the doctor didn't really tell more information about it):

Sympathetic neurons were placed in a TC system that allowed the somas (cell body) and neuritis (axons) to be bathed in different media.

- look at the figure below:



- In the right: Neurons can be kept alive by adding NGF only to the compartments with growing neurites.

- In the left: Most neurons die when grown without NGF for 30 hr.

- In both cases, anti-NGF prevented TrkA activation in the central compartment (from slides).

* Remember the general principle here in simple words; that what work will survive and what doesn't work will die end be eliminated. So, each neuron survival and function depends on the neuron previous to it (because it delivers the AP), so the neuron sends BDNF to the previous neuron and both survive.

****BDNF** is important in many psychological functions and the most important one is the memory that we will discuss.

Memory

- Before, we talked about memory and said it facilitated circuit.

- We have two types of memory:

Declarative memory and non-declarative memory.

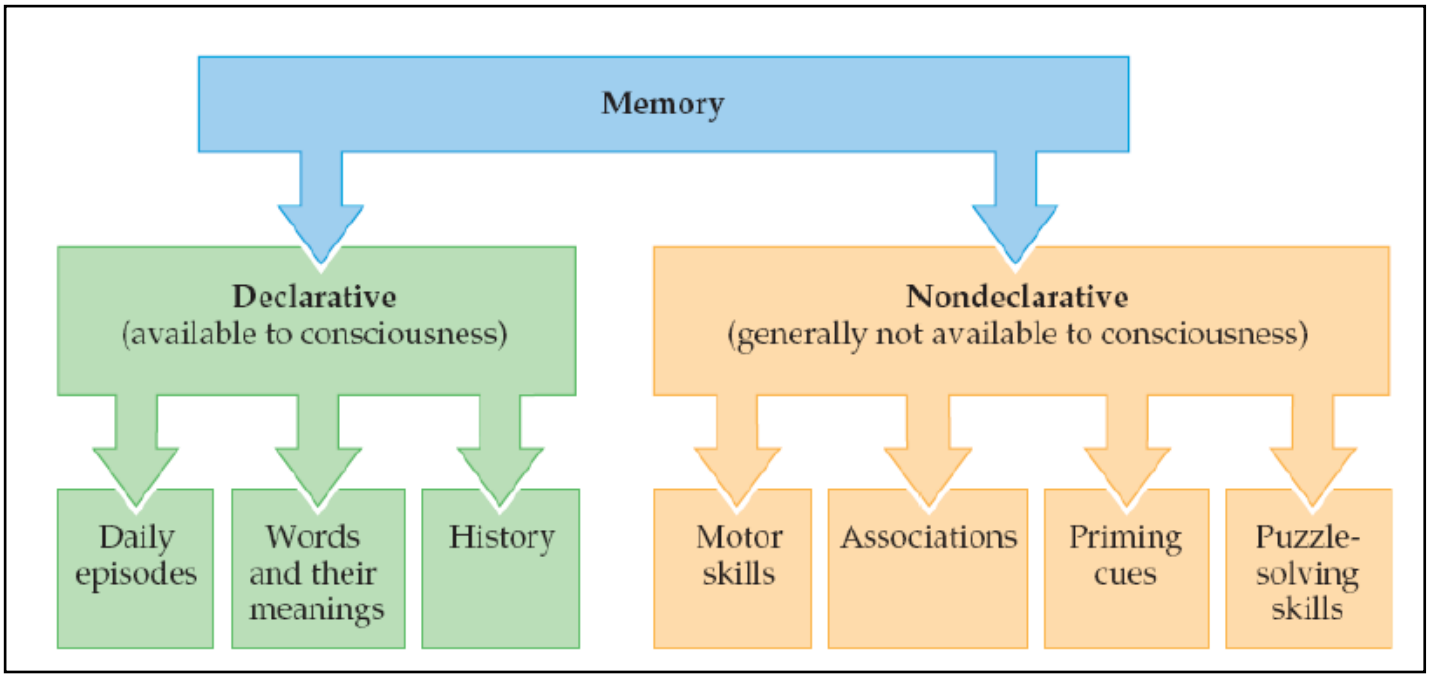
1) Declarative(general facts) >> early memory It includes the answers for any question [what is your name, in which university…etc.]. Giving you fast answers and explanations. It has special site in the brain, stored in the cortex. Which is available to consciousness.

2) Non- declarative >>which is not available to consciousness, it related to classical conditioning

Remember the example of training the dog to produce saliva in response to the bells sound!

Here we remember things not related to questions. Like: Motor skills, puzzle solving skills ……

- Most importantly this type of memory not stored in the cortex.



- We more concern about the declarative memory since it stored in the cortex.

** We also classify the memory into two types, relating to the time into:

1- Long term memory: when you repeat and memorize a piece of information, it will last from days to years. For example: you always remember your ID number.

2- Short term memory: it's the working memory, when you hear information you will remember it for seconds in the meantime then you will forget it.

** keep in mind when wither the memory is long or short memory it stills facilitated circuit.

** When you hear for example your college ID number (short term memory) for the 1st time it will go to the association cortex in a certain sequence activating certain neurons, they will remain active as long as the prefrontal cortex keeps attention to this information. Once you give your attention to another thing the prefrontal cortex through Ach & norepinephrine will make attention and activate another area or neurons, the memory of your college ID number will fade away and you no longer remember it. But if you want this memory to be long term memory the prefrontal area will give attention to the area where you calculate and remember numbers so this makes remembering your college ID number easier.

From short term to long term memory?

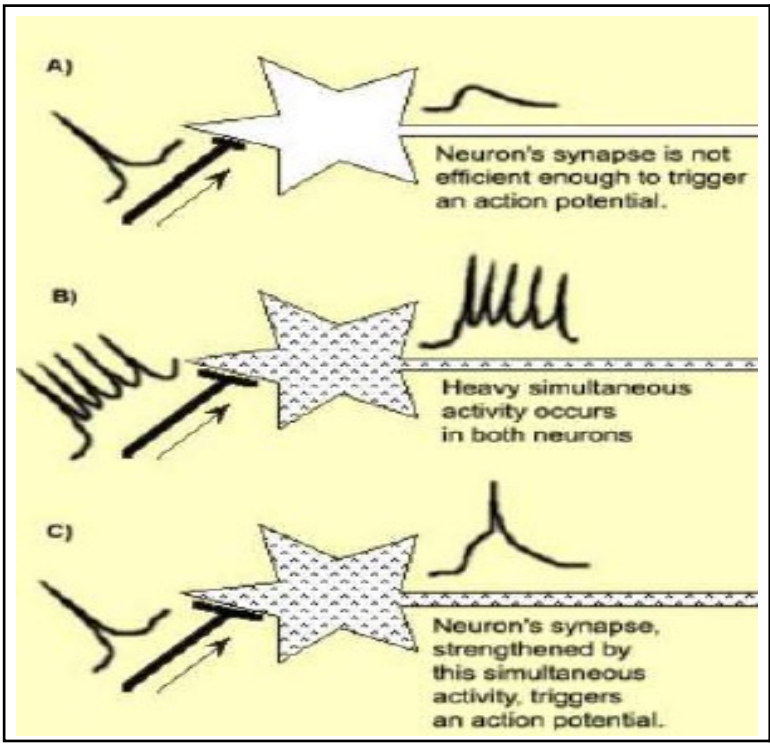
facilitated circuit must be for long time (i.e. time-dependent; repeated stimulus) How?

When action potential reaches **certain area,** it will go through neurons in the sequence we want, to guarantee the potentiation of electrical activity in this area to be strong, fast and good (explained below)

- We know that action potential in the 1st neuron will produce postsynaptic potential on the 2nd neuron that may lead **to action potential or not. Since** I need electrical potentiation and easier facilitated circuit to develop, the neuron must give multi synapse to more than one neuron and make it the main pathway therefore, **the early action potential** on the pre- synaptic will cause action potential in the post synaptic and this what we called **long term potentiation**.

- At first it was post synaptic that give graded potential but with **repetitive activity** long term potentiation produced between two neurons, so **the same action potential** will give action potential on post synaptic.

- It's the three synaptic (in circuit) but a persistent strengthening of synapses occurs that produce a long-lasting increase in signal transmission between two neurons.



In this figure:

-in A: its normal synapse between two neurons where the synapse not efficient and graded potential produced in the postsynaptic.

- In B: when the stimulant is strong in both neurons that produce an action potential in the post synaptic.

- In C: synapse is strengthened by simultaneous activity that makes the same action potential give action potential in postsynaptic.

** Fort this circuit to be a permanent circuit; this electrophysiological conversion must be associated with anatomical one that include molecular, anatomical and chemical changes.

** The first anatomical association is **bigger and more numbers of spines**. When they look at the dendrites and cell body from anatomical view, they find small dots and buds like structure on them which are spines.

- Spines are the region where the two neurons synapse, between dendrites and axon terminal. So through these spines Pre synaptic neuron can give axon terminals to the postsynaptic neuron 30 or 40 instead of 20 for example (they increase in numbers), or the number of axon terminals remain the same 20 terminals but the one terminal axon instead of being 1 microns it becomes 10 microns.

-Synapse becomes bigger with more receptors so more graded potential that will become for sure action potential.

** So spines make:

Synapse bigger, more receptors on the postsynaptic, more neurotransmitter releasing so more action potential.

** Since these spines related to anatomical changes there must be chemicals that induces such changes. We already talked about one of them which is BDNF, BDNF make the previous neuron survive and getting bigger. So BDNF has a crucial rule for learning and memory.

** Remember when you graduate you may forget your ID number because this circle is no longer active for a period, in this period of time where no behave occur on the neuron, the neuron will decrease in size and reduce the synaptic activity making you store another new formation like your new mobile number.

- Since these anatomical changes need BDNF, we need

Ca for releasing BDNF from postsynaptic to presynaptic

- Even if we have glutamate receptors, small activation won't release Ca, since the AMPA will open without NMDA receptor.

- So that why they tell you to repeat memorizing something since it's induce your memory.

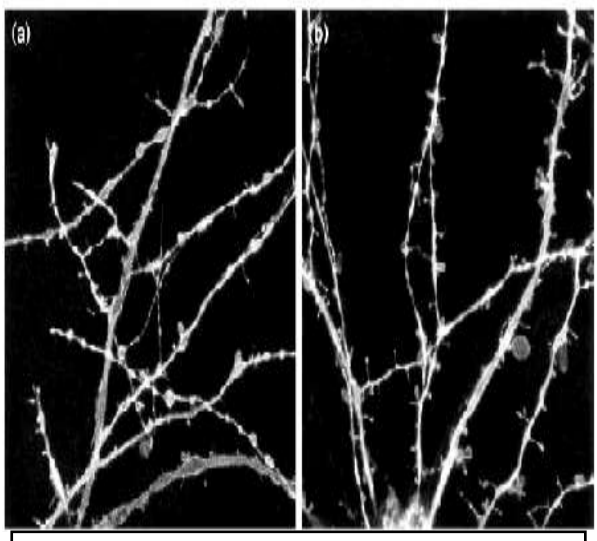


Figure for spines

- There are modulators come from outside the cortex
and have relations with Ca, mainly serotonin &
norepinephrine, this describe the reason of remembering
a situation even if it happen once in the life because when it happens you were extremely happy or feeling other things and this related to serotonin , norepinephrine & NO secretion, and since they have receptor that related to Ca releasing, they will cause more releasing of BDNF.

So this memory becomes unforgettable memory to you.

* Students questions:

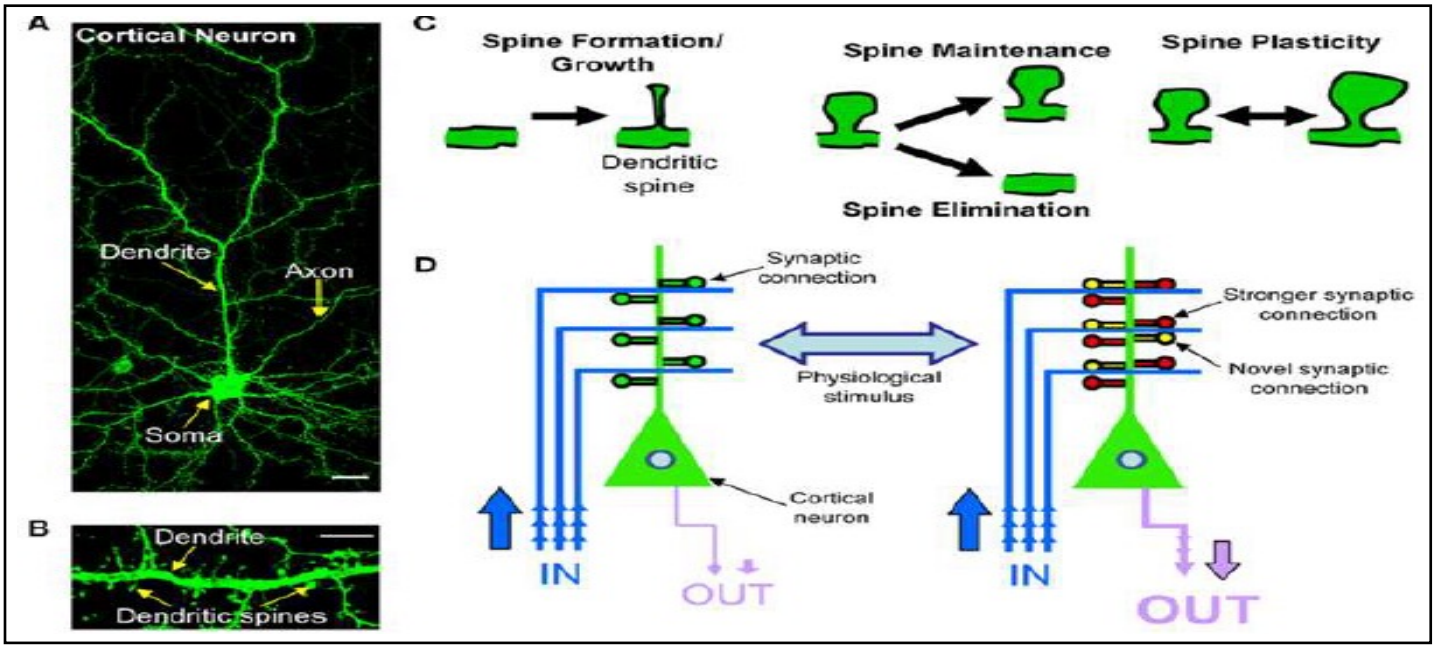
Q1: Is it possible for this synapse to disappear?

Yes, if this memory is no longer used so no activation for it, no signal for surviving and the synapse start to shrink.

Q2: How the brain store the memories and differentiate between what happened before 4 years and what happened last month?

It's the function of the prefrontal that make selection attention and maestro of the memories in time and place.

** Look at the figure below which summarizes what we talked about:



EEG and brain waves

- EEG is Electroencephalography; it's a monitoring method to record electrical activity of the brain. The activity that recorded doesn't resemble action potential or excitation or inhibition.

- It tells you if these neurons are *active or not*.

- Since we have more than one layer between the electrodes and the skull itself, it needs big numbers of neurons to be active to give a record.

- Although it's a complex wave, it still has a specific frequency.

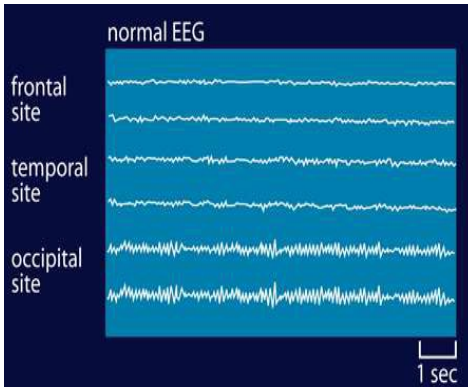
We classify them according to high or low frequency.

* **Frequency**: the number of oscillations/waves per second,

measured in Hertz (Hz), it reflects the firing rate of neurons.

- The waves are classified according to frequency into:

alpha, beta, theta, delta



1) Delta Waves:

-They are slowest wave 1– 3 Hz. There are big numbers of activated neurons but they act slowly so less action potential.

- They recorded when the cortex not very active:

Like deep, dreamless sleep, not moving, not attentive,

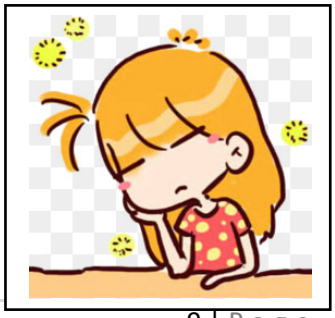
Sleeping or comma.

2) Theta Waves:

- Slow wave frequency: 4 – 8 Hz.

- The cortex not completely at sleep, between sleeping and waking "Drowsy", there is little brain activity, in deep meditation without thinking.

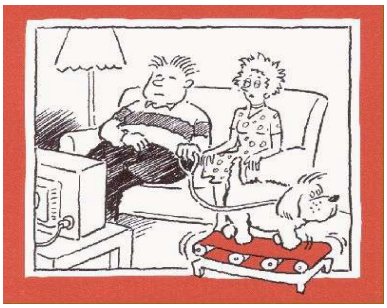
- And when internal focus, and prayer; subconsciousness.



3) Alpha Waves:

- Mid wave frequency: 8 – 13 Hz, brain *is very active* and makes *processing* but not that heavy process it's just normal processing.

- In relaxing situation, the dominants are *Parietal and occipital lobes* since they are not completely shut down (where vision make processing)



- Recorded in Relaxing, watching television, light reading (e.g., novel), eyes closed and even when you trying to keep focus

In the lectures.

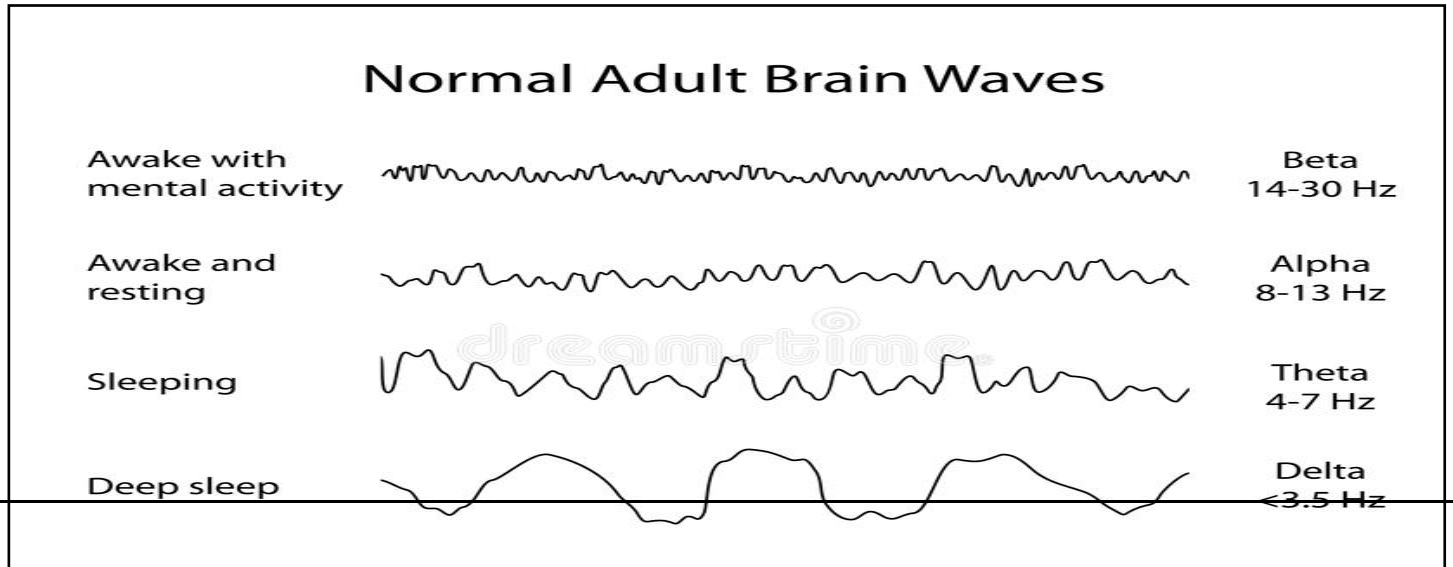
4) Beta Waves:

- High wave frequency: 12 – 35 Hz, recorded in our highest activity when you are doing you tasks and job.

- So if you were given a puzzle to solve, Beta waves will be recorded from the dominant prefrontal cortex. Or if you listening to something and you were trying to understand and keep attention to it, your beta waves will be recorded from the auditory cortex.

- So in general these waves recorded in listening and thinking during analytical problem solving, judgment, decision making, and processing information.

** look at the figure below that shows the difference between these waves:



Sleep

** Why Do We Need Sleep?

- We don't sleep for brain resting!! We sleep for:

1- Adaptive Evolutionary Function:

-Safety and energy conservation/ efficiency.

2- Restorative Function:

- Body rejuvenation & growth.

3- Brain Plasticity

- Enhances synaptic connections and memory consolidation through synapsing and take the decision of the importance of these memories.

** There are two systems one tries to awake the brain and the other try to make it sleep:

- The one that try to awake the brain in the past it was named **reticular activating systems** which is a group of neurons found in the brainstem. Nowadays with technology and better staining they found that this system is the same as:

1- *raphe nucleus* that gives serotonin, 2-locus corelus that give norepinephrine , 3- the centers that produce Ach (their names not for memorizing),

so **reticular activating systems** composed of the nuclei that secrete the brain modulators that waking up the brain like **Ach, norepinephrine, serotonin, histamine and dopamine.**

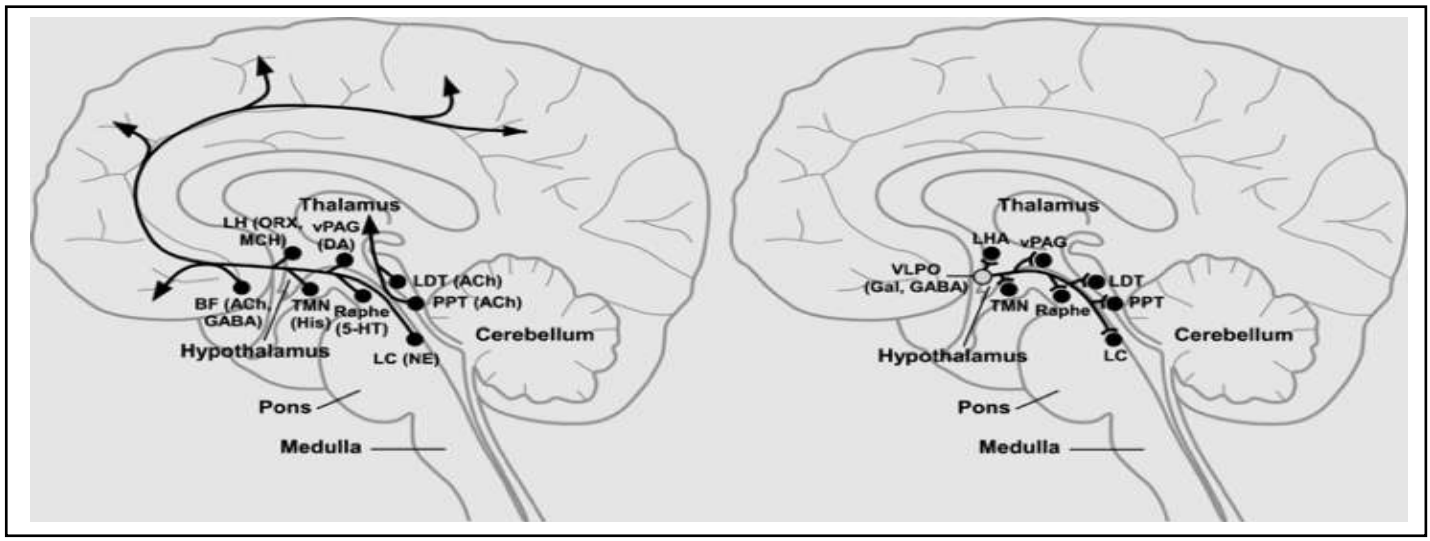
- The other system that turning off the brain which is inhibitory in nature, it's the VLPO. VLPO is a center found in the base of the brain near the hypothalamus that secretes the main inhibitory GABA, GABA turns off the cortex and the CNS by inhibiting the activating centers (reticular activating system).

*These two systems are the main systems but we have other systems that activate the activating system or activate the inhibitory system in order to induce or reduce sleep.

- For example if someone feeling pain, he can't sleep because the pain goes to the reticular system through spinal reticular tract activating it, so the centers of this system get activated and he will remain awake. It's the same when you hear loud noises that prevent you from sleeping since it will go through sensation and activate these centers.

- Some pains appear in the night only because these centers are highly activating during the day once the night enter their activities will reduce. Raphe nucleus and locus corelus will secrete less serotonin and norepinephrine making the patient feel the pain more, like toothache.

** look at the figure below that shows the two systems:



** **Hypocreatin (orexin),** is another system that activate the activating system or inhibit the VLPO, it considered waking up system.

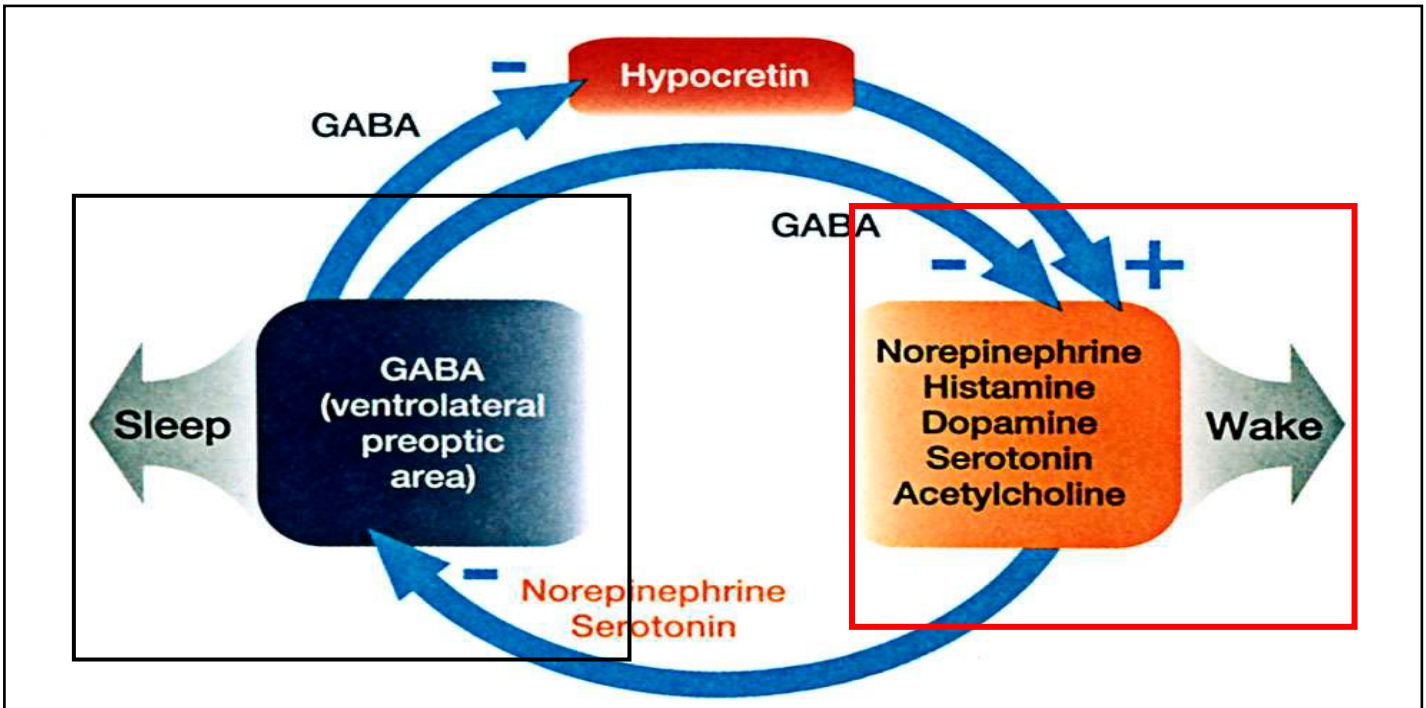
** In opposite to this system is the neurotransmitter that released from the pineal gland which is **melatonin**, it's one of the important regulators of circadian rhythm so it increases in night.

Pineal gland doesn't have sensory for light, so during the day, vision will give signals to the supraoptic nucleus of the hypothalamus that will intern inhibit the pineal gland so the amount of melatonin decrease. While in the night the inhibition on the pineal gland will disappear so it starts to secrete melatonin. Melatonin will inhibit the reticular activating system and activate the VLPO center and then make you sleep.

- Suprachiasmatic nucleus it's a nucleus situated atop the optic chiasm responsible for organizing circadian rhythms.

- So people who travel long-distance trans-meridian (jet lag) crossing many hours in the day, their sleep will be none organized and Intermittent sleep so they advised to take melatonin supplements.

** Look at the figure below and its description:



In this figure:

- in the red square anything that increase reticular system or decrease inhibitor system it will lead to lack of sleep and this condition named insomnia.

- in the other square anything that decrease reticular system or increase inhibitor system it will lead to over sleep this condition named Narcolepsy, this also apply to patient who was setting then suddenly fell asleep.

**we concern more about GABA since it's the main inhibitor, so melatonin only an effector &modulator.

Coffee

- One of the effectors doesn't act on the receptors directly.

- One of the regulators that induce or reduce sleep is the brain activity; if the brain was tired, it will induce sleep.

- When the brain activity increases, the neurotransmitter *adenosine* amount will be increased. Adenosine binds to A1 receptors (adenosine receptor), this receptor is an inhibitory receptor that will increase adenosine and inhibit the cells that contain A1 receptor.

- A1 receptor found a lot in Ach producing neurons in basal ganglia and brainstem, so according to that if adenosine increase→ Ach activity will decrease. Decrease activity of Ach will decrease sensory for perception and sustain attention, so patient can't focus although he trying to and can't make good processing, he feels sleepy.

- In another hand when Ach activity decrease and if you drink coffee, red bull or any drink that contains Caffeine and Theophylline, it will make you awake (مصحصح) even though the high amount of adenosine is still there. This occur because they are A1 antagonist, so adenosine no longer inhibit Ach then Ach level will increase making you more focused, attention and awake.

Sleep stages

- Sleep is divided mainly to two stages which are:

a) Slow waves sleep or non- REM sleep.

b) Deep sleep or rapid eye movements sleep (REM sleep).

- sleep start from waking up then brain turn off the areas slowly and decrease their processing entering stage 1,2,3, then 4 where almost all the activating system and cortex turning off then REM sleep start where the brain do its cleaning and functions (remember when we talked about the purpose of sleeping !!). So if you sleep until stage 4 do you benefit from this sleep?

No, because you don't enter the most important and beneficial stage where the brain do its job which is the REM sleep. Even if someone sleep for 8 hours & he didn't enter REM stage, then he will suffer from insomnia, according to that REM sleep doesn't related to how much hours do you sleep it's all about how much REM sleep you get.

- There are sleep LABs where you can know the amount and stages of sleep that the patient gets, especially in patients who has sleep deprivation or sleep apnea, when patients sleep for 8 hours but before they reach the REM sleep they suddenly wake up and they suffer from tiredness, headache, dizziness and lack of attention.

- Stage 1 – eyes are closed, relaxation begins and starts feeling a little sleepy; the EEG shows alpha waves; one can be easily aroused.
- Stage 2 – brain turn off more areas, EEG pattern is irregular with sleep spindles (high-voltage wave bursts) and person start to sleep with decrease in vital function like breathing; arousal is more difficult, person needs strong stimulus.

- Stage 3 – brain turn off more and more areas (big part from the brain turned off and the other part still active), sleep deepens; theta and delta slow waves appear; vital signs decline; decrease muscle activity; dreaming is common. If all the brain turned off except the vision it's still active and make processing, it will appear as you see things so you are dreaming same to hearing. If motor tone or center still active, then you can move while sleeping even respond if someone talking to you but without filter or without your realizing this called sleep talking. If the conscious center was the first to shut down before motor, person will walk while sleeping.
  ** Through brain development the prefrontal is less active, so children from age 6-12 years were sleep walking but it will disappear with age.
- Stage 4 – EEG pattern is dominated by delta waves; skeletal muscles are relaxed; arousal is difficult.

Then REM sleep will be entered.

REM sleep

- Presence of beta activity (desynchronized EEG pattern).

- Physiological arousal threshold increases since the brain is active:
Heart-rate quickens, breathing more irregular and rapid, Brainwave activity resembles wakefulness, Genital arousal and Loss of muscle tone (paralysis).

- Vivid, emotional dreams.

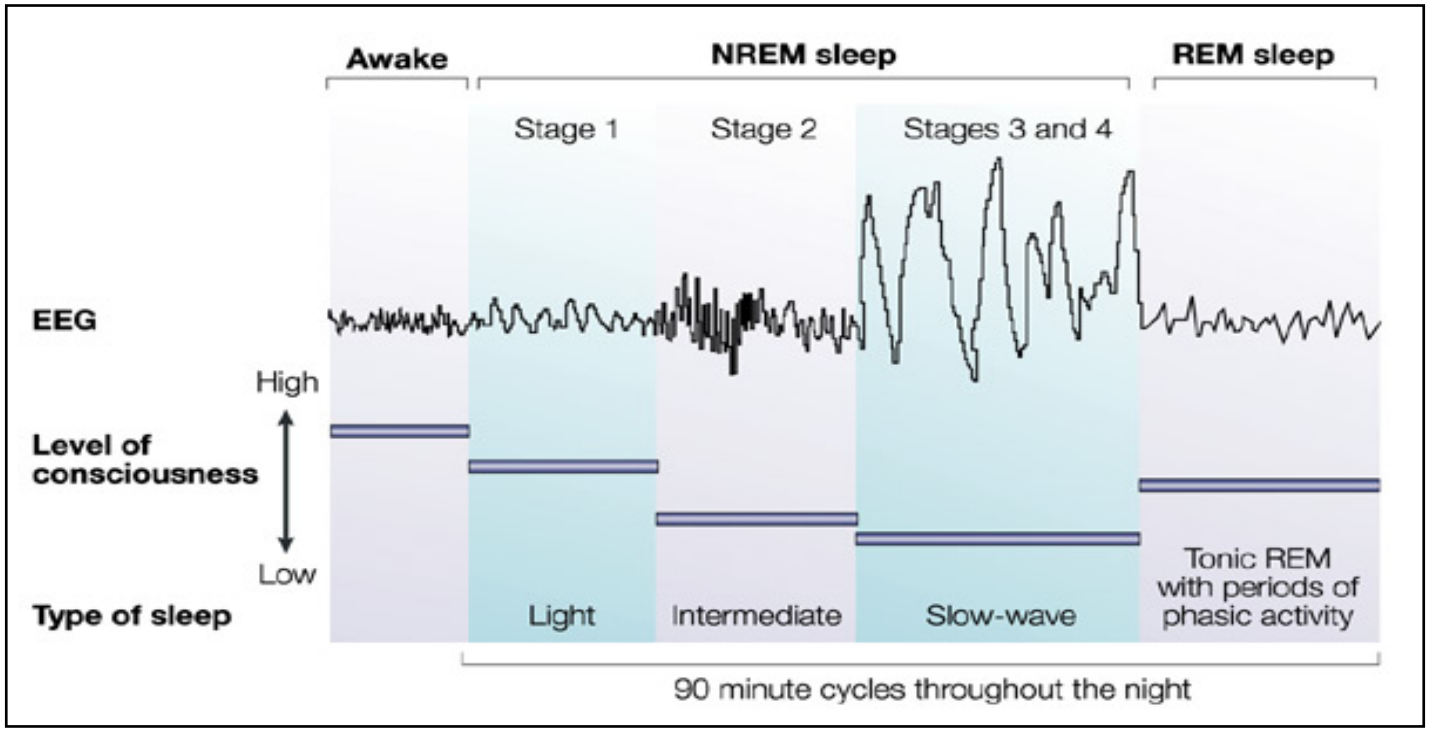
- May be involved in memory consolidation.
- patient with sleep apnea when the reaches REM sleep after the stages of slow waves, if he has closure in the airway so no oxygen for the brain activity, the brain will consider it as danger making him wake up in order to fix the closure of the airway, here the patient goes back to stage one and two. Then he will reach the REM sleep and wake up again and so on. Although he sleeps for 8 hours but he never enters REM sleep.

** Every stage from the beginning of sleep to the end of REM sleep is considered as sleep cycle.

** Normal person has from 3-5 sleep cycles in average for 8 hours.

** Remember these cycles not necessary have the same time or percentage of REM sleep in each one of them to be the same.

** Look at the figure below it shows the sleep stages and EEG waves:



**We need REM sleep more, so in early life brain develop and learn more so REM & general sleep will be more.

** With aging total amount of sleep decrease and the REM sleep decrease more.

** If you were being waking up all the night, in the next night you will sleep and enter REM sleep faster, even the percentage of REM sleep will be more since you didn't get enough sleep in the previous night.

** The night where you study hard, trying to remember general information and learning new things, you will inter REM sleep directly and its percentages will be more.

Please refer to the slides

Sorry for any mistakes