Physiology of the sleep

Objectives:

- ***Explain the difference between sleep and coma.***
- ***Define what is meant by NREM (non-rapid eye movement, SWS) and REM (rapid eye movement) sleep.***
- ***Describe how NREM and REM sleep are distributed during a normal night sleep in the average adult human***
- ***Describe the behavioral and autonomic features associated with NREM and REM sleep.***
- ***Describe how the EEG, as a physiological tool, is being used to delineate in which stage of sleep (or wakefulness) a person is.***
- ***Appreciate how the total sleep duration and different sleep stages vary with different ages in normal humans.***
- ***Describe the current theories about the neural basis of sleep.***
- Sleep disorder
- Physiological mechanism of sleep and waking

Bold & Italic objectives are included in the medical education guide

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❖ Terminology

Terminology	Definition
R.E.M "Rapid eye movement"	a kind of sleep that occurs at intervals during the night and is characterized by rapid eye movements, more dreaming and faster pulse and breathing.
NREM "Non rapid eye movement"	Also called "SWS (Slow-Wave Sleep)" A stage where sleep EEG waves are generally of low frequency, and is not associated with rapid eye movements . Waves are generally of low frequency
Sleep	- State of unconsciousness from which a subject can be aroused by appropriate sensory or other stimuli. - a normal, periodic, inhibition of the reticular Activating system.
Awake	State of readiness/alertness & ability to react consciously to various stimuli.
Coma	State of unconsciousness from which a person cannot be aroused by any external stimuli.

Why do we sleep?

- Sleep theory #1- To Rest: to gain relief from this hyperactive state
- Sleep theory #2 - To Heal : sleep also allows us to heal our bodies. The immune system (our ability to fight disease) sleep deprivation affects our metabolism (our internal chemical reactions). It may also help us save energy for when most need it.
- Sleep theory #3- To Learn: sleep may help the human brain get better organized - by filing away important memories and discarding unwanted information.
- Sleep theory #4 - To Dream : Dreaming appears to be a by-product of REM sleep. So is it possible that the main reason why we sleep is to dream? If so, why do we dream?

Ultimate:

- sustains our ability to reproduce successfully, by maintaining good health.

Sleep has been postulated to serve many functions:

1. **neural maturation**
2. **facilitation of learning or memory**
3. **cognition**
4. **clearance of metabolic waste products**
5. **conservation of metabolic energy.**

Theories of sleep:

Preservation & protection theory

Sleep preserves energy and it provides protection.

* For example, both body temperature and caloric demand decrease during sleep,as compared to wakefulness

Restoration theory:

Body wears out during the day and sleep is necessary to put it back in shape.This is supported by findings that many of the major restorative functions in the body like muscle growth, tissue repair, protein synthesis, and growth hormone release occur mostly, or in some cases only, during sleep

❖ Describe how the EEG is being used to delineate in which stage of sleep a person is

EEG (electroencephalogram) waves: Before you start you have to know these different types of wave generally		
Alpha activity	smooth electrical activity of 8–12 Hz	generally associated with a state of relaxation.
Beta activity	Irregular electrical activity of 13–30 Hz	generally associated with a state of arousal (when you're thinking or concentrated).
Theta activity	EEG activity of 3.5–7.5 Hz	that occurs intermittently during early stages of SWS & REM sleep.
Delta activity	Regular, synchronous electrical activity of <4 Hz recorded from the brain	occurs during deepest stages of SWS.

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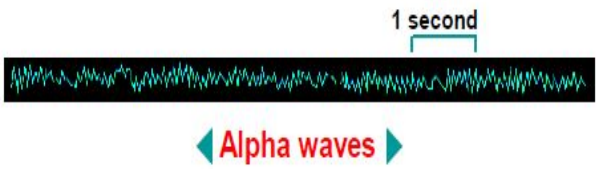
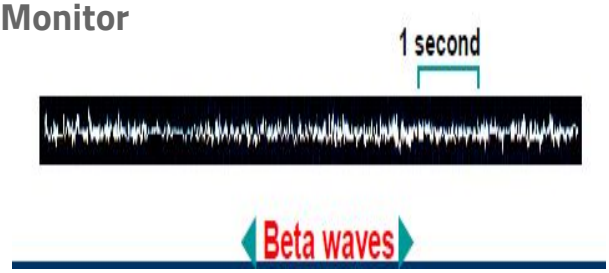


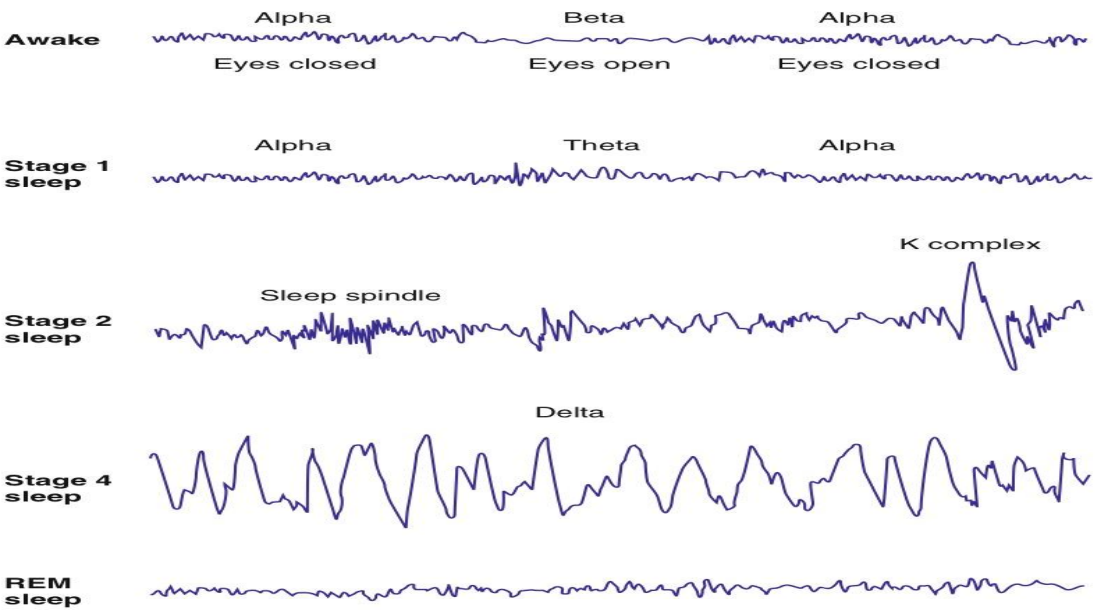


EEG WAVES In wakefulness

Awake, but non-attentive, large, regular alpha waves

Awake and attentive - low amplitude, fast, irregular beta waves

❖ Describe how the EEG is being used to delineate in which stage of sleep a person is

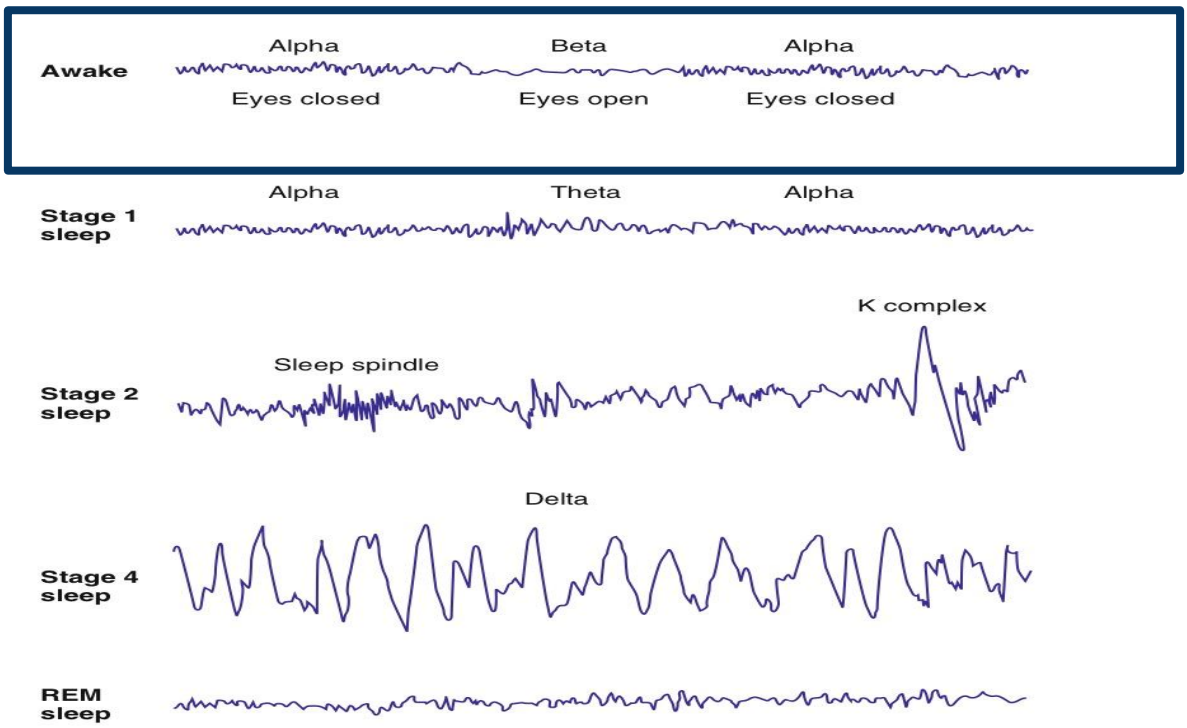


The electroencephalogram (EEG) records electrical activity of the cerebral cortex **via electrodes placed on the skull**. The EEG waves originate from alternating excitatory and inhibitory synaptic potentials that produce sufficient **extracellular current flow across the cortex** to be detected by surface electrodes. (EEG waves are not action potentials. Electrodes on the surface of the skull are not sufficiently sensitive to detect the small voltage changes of single action potentials.)

The normal EEG (Fig. 3-35) comprises waves with various amplitudes and frequencies. In **a normal, awake** adult **with eyes open,** the dominant frequency recorded over the parietal and occipital lobes is the **beta rhythm** (13–30 Hz), which consists of desynchro- nonous low-voltage, high-frequency waves. **With eyes closed,** the dominant frequency is the **alpha rhythm** (8–13 Hz), which has more synchronous waves of higher voltage and lower frequency.

As a person falls asleep, he or she **passes through four stages** of **slow-wave sleep**. **In Stage 1**, the alpha waves seen in an awake adult with **eyes closed** are **interspersed-** بتتخللها with lower-frequency **theta** waves. **In Stage** 2, these low-frequency waves are interspersed with high-frequency bursts called **sleep spindles and large, slow potentials called K complexes**. **In Stage 3** (not shown in the figure), there are very low-frequency delta waves and occasional sleep spindles. **Stage 4** is characterized by **delta** waves. Approximately every 90 minutes, the slow-wave sleep pattern changes to rapid eye movement (REM) sleep, in which the EEG becomes desynchronized, with low-voltage, high-frequency waves that resemble those in an awake person. **REM sleep is sometimes called paradoxical** sleep:Even though the EEG is most similar to that of the awake state, the person is (paradoxically) most difficult to awaken. **REM** sleep is **characterized** by loss of muscle tone, notably in the eye muscles resulting in rapid eye movements, loss of temperature regulation, pupillary constriction, penile erection**,** and fluctuations in heart rate, blood pressure, and respiration. Most dreams occur during REM sleep. The proportion of slow-wave sleep and REM sleep varies over the life span. Newborns spend half of their sleep in REM sleep; young adults spend about 25% of sleep in REM sleep; and the elderly have little REM sleep.

❖ Describe how the EEG is being used to delineate in which stage of sleep a person is



When the awake person's attention is directed to some specific type of mental activity, **the alpha** waves are replaced by *asynchronous, higher frequency but lower voltage beta waves.* Note that the visual sensations cause **immediate cessation** of the alpha waves and that these waves are replaced by low-voltage, asynchronous beta waves.

EEG patterns from a typical person in different stages of wakefulness and sleep. **Alert wakefulness** is characterized by high-frequency beta waves,whereas **quiet wakefulness** is usually associated with alpha wave.

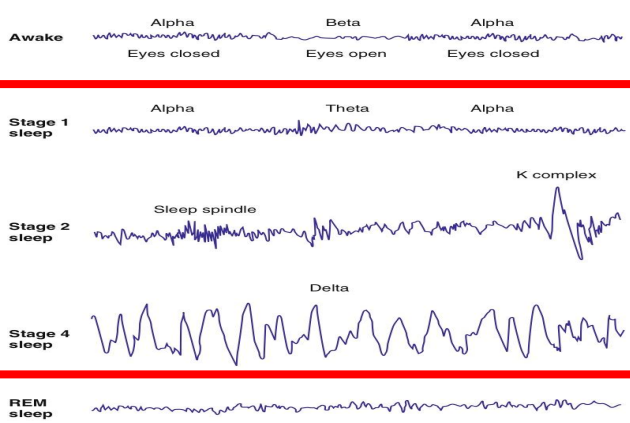
Do you notice the similarity between awake & REM sleep waves?

It is often difficult to tell the difference between this brain wave pattern and that of an awake, active person. The waves are irregular and of high frequency, which are normally suggestive of desynchronized nervous activity as found in the awake state. Therefore, REM sleep is frequently called desynchronized sleep because there is lack of synchrony in the firing of the neurons despite significant brain activity.

❖ Describe how the EEG is being used to delineate in which stage of sleep a person is

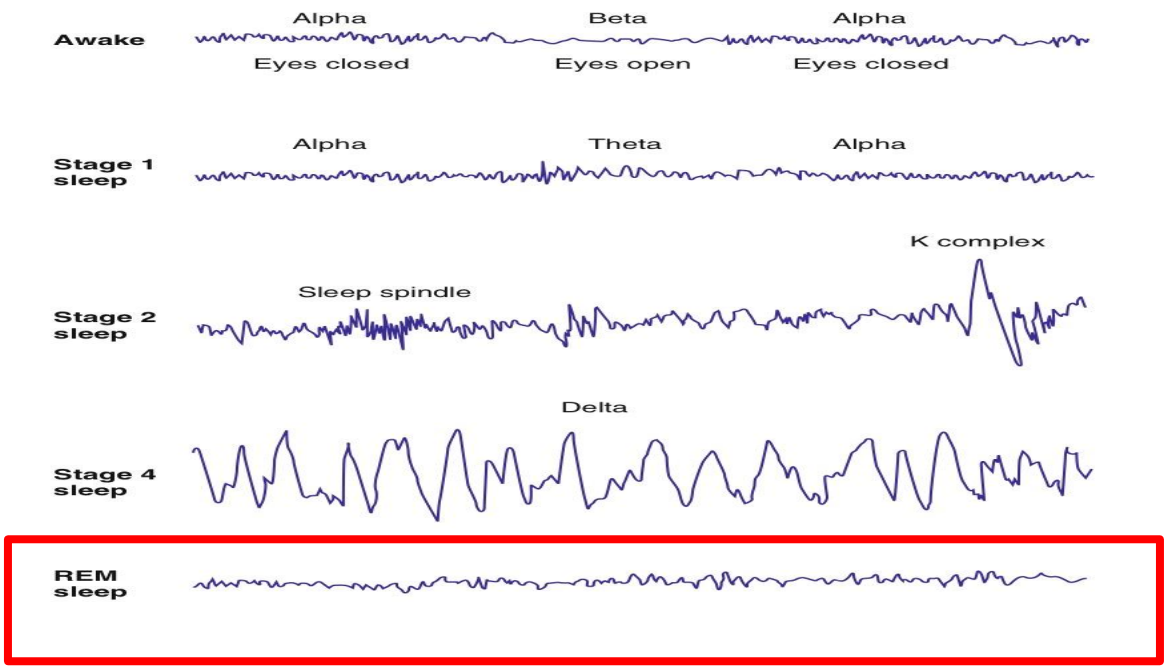
Sleep Classification is Based on EEG Features

	A)NREM sleep		
	Stage 1	**Stage 2**	**Stage 3&4**
Experience	**Falling asleep** and transition stage between waking & sleep.	Base line of sleep **This is the first stage of true sleep.**	Deep sleep
duration	1-5 minutes. ~2.5% of a normal night sleep.	90 minutes. - ~45-60% of a normal night sleep	- 15-30 minutes. - ~40% of all sleep.
signs	Eye begins to roll slightly	-	Slowing of heart rate, breathing rate, and brain activity **Body temperature begin to fall. BP decreases. Difficult to awaken the person.**
waveform	Irregular, jagged, low-voltage wave Alpha waves& theta waves appear on EEG	- **Sleep spindles** These are bursts of alpha-like 10-14 z, 50 uV waves **.** -**K-complex**	**Stage 3**: **This stage occurs about 20-25 min after falling asleep.Lower frequency (mainly theta), higher amplitude EEG waves.** **Stage4**: **Still slower frequency (mainly delta) & still higher amplitude waves**
notes	Start when sleep has just begun, brain activity begins to decline **Lasts 1-7 mins. (if you ask, person will say he is awake**		As the night goes on there is progressive **reduction** in stages 3 and 4 sleep and progressive **increase** in REM sleep.



❖ Describe how the EEG is being used to delineate in which stage of sleep a person is

	B)REM sleep
Experience	Very active stage of dream Vivid dreams can occur
duration	20-25% of normal night sleep
waveform	Irregular, low-volatge and fast activity
	Beta waves
Notes	Length of REM stages increases as the night progresses (it means the duration of REM increases every cycle during long night sleep). **Heart rate and respiration become irregular** **The difference is that the dreams in SWS are not remembered but in REM, dreams can be remembered too important !!**



❖ Describe how NREM and REM sleep are distributed during a normal night sleep in the average adult human

Distribution of Sleep Stages

- SWS occupies most of the total night sleep time (around 75-80%) , it is interrupted by intervening REM sleep periods, approximately every 90 minutes .
- **In a typical night of sleep:**

- young adult first enters NREM sleep, passes through stages 1 , 2 , 3 and 4 SWS, then, 60-100 min from sleep onset, goes into the first REM sleep episode
- This cycle is repeated at intervals of about 90 min throughout the 8 hours of night sleep.
- **There are 4-6 sleep cycles per night** (& 4-6 REM periods per night)
- As the night goes on there is progressive reduction in stages 3 & 4 sleep and a progressive ↑ in REM sleep .

REM Sleep (Paradoxical Sleep) because it is a paradox that a person can still be asleep despite the presence of marked activity in the brain.

- **In a normal night of sleep,**

- episodes of REM sleep lasting 5 to 30 minutes usually appear on the average every 90 minutes.
- REM sleep is not as restful as SWS .
- When the person is extremely sleepy(مرهق), each episode of REM sleep is short, and it may even be absent.
- Conversely, as the person becomes more rested through the night, the **<u>durations</u>** of the REM episodes increase.

- ***Characteristics of REM sleep*:**

1. There are rapid eye movements .(Neurons of the pons)
2. Muscle tone throughout the body (except eye muscles) is exceedingly depressed

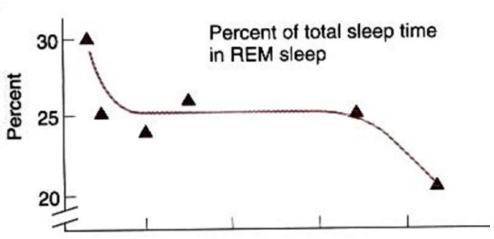
How the occurrence of REM sleep increase?. Acetylcholine secreting neurons activate many portions of the brain.Even though the signals are not channeled appropriately in the brain to cause normal conscious awareness that is characteristic of wakefulness-drugs that mimic the action of acetylcholine

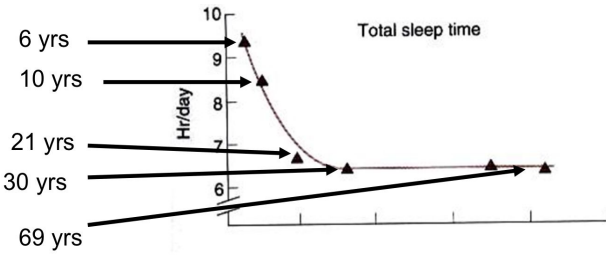
- **REM sleep is a type of sleep in which the brain is quite active, but this brain is:**

1. is not aware cut-off the external world.
2. its activity is not channeled into purposeful external motor activity.

❖ Appreciate how the total sleep duration and different sleep stages vary with different ages in normal humans.

Normal sleep cycle at different ages:





	REM step occupies (explain percent of total sleep time in R.E.M. Sleep)
Premature infants	80% of total sleep.
Full-term neonates	50% of total sleep.
Elderly from 20-69ys	20% of total sleep.
Children	More sleep time and stage 4 than adults.

This table explains how many hours do we need to sleep ?

New born	15 - 20 hours
Children	10 - 15 hours
adult	6 - 9 hours
Old age	5 - 6 hours

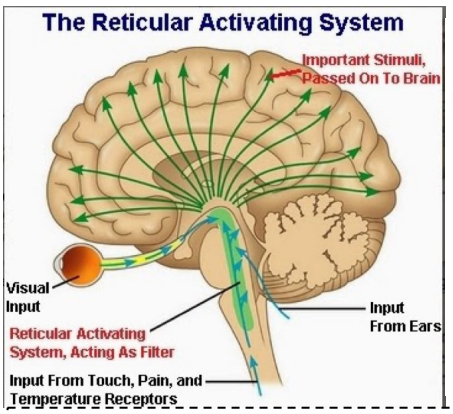
For your information

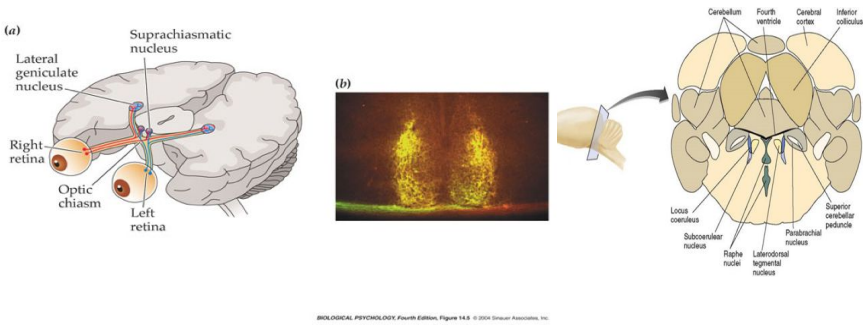
❖ Describe the behavioral and autonomic features associated with NREM and REM sleep

(Dr Nervana said just read the table).

TABLE 14.2 *Neural Activity of Neurotransmitter Systems during Sleep and Arousal*

Neurotransmitter	Site of cell bodies	Activity during		
		Wakefulness	SWS	REM
Serotonin	Raphe nuclei	High	Low	Very low
Norepinephrine	Locus coeruleus	High	Low	Very low
Acetylcholine	Brainstem	High	Low	High





A diffuse network of nerve pathways in the brainstem connecting the spinal cord, cerebrum, and cerebellum, and mediating the overall level of consciousness. RAS is the **primary** centre of sleep

- Describe the behavioral and autonomic features associated with NREM and REM sleep. This is important.

PHYSIOLOGICAL CHANGES IN SLEEP	
CVS:	Pulse Rate, cardiac output, blood pressure & vasomotor tone are decreased but the *blood volume* is increased
Respiration	Tidal volume & respiratory rate are decreased. BMR is decreased 10-15%.
Urine volume:	decreased.
Secretions	Salivary/lacrimal secretions are reduced, gastric/sweat secretions are increased

These are the **overall changes** during sleep, REM sleep can be different

TABLE 14.1 *Properties of Slow-Wave and REM Sleep*

Property	Slow-wave sleep	REM sleep
AUTONOMIC ACTIVITIES		
Heart rate	Slow decline	Variable with high bursts
Respiration	Slow decline	Variable with high bursts
Thermoregulation	Maintained	Impaired
Brain temperature	Decreased	Increased
Cerebral blood flow	Reduced	High
SKELETAL MUSCULAR SYSTEM		
Postural tension	Progressively reduced	Eliminated
Knee jerk reflex	Normal	Suppressed
Phasic twitches	Reduced	Increased
Eye movements	Infrequent, slow, uncoordinated	Rapid, coordinated
COGNITIVE STATE	Vague thoughts	Vivid dreams, well organized
HORMONE SECRETION		
Growth hormone secretion	High	Low
NEURAL FIRING RATES		
Cerebral cortex (sustained) activity	Many cells reduced and more phasic	Increased firing rates; tonic
EVENT-RELATED POTENTIALS		
Sensory-evoked	Large	Reduced

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Table 14.1 © Sinauer Associates, Inc.

كلهم معنا لكن الدكتورة كانت حاطة أسهم على المربعات الحمراء

❖ Describe the current theories about the neural basis of sleep. (DR. Nervana said just read them)!

Theories of Sleep

Although several theories of sleep have been proposed, most current evidence is in favor of the following:

1. **Serotonin**, produced by the Raphe Nuclei, induces **SWS** sleep.
2. The mechanism that triggers REM sleep is located in the Pontine Reticular Formation & the Ponto-Geniculo-Occipital circuit is instrumental in generation of REM sleep.
3. **The hormone Melatonin (released from Pineal Gland) plays an important role in day-night alternation of sleep.**

Role of Serotonin & Melatonin in SWS:

Raphe nucleus(secret serotonin):

Stimulation of Raphe Nuclei (**in the lower pons & medulla**) **induces SWS**

- Destruction of the Raphe Nuclei renders the animal **sleepless** for several days until it dies.Administration of drugs that **block serotonin** formation make the animal sleepless for several days.
- **Transecting the brainstem at the level of the mid pons**, leaves the animal in a state of intense wakefulness for a period of days.(The transection cuts the nerves going from the inhibitory serotonin-secreting Raphe Nuclei to the Bulboreticular Facilitatory area of the RAS).
- Indication that the serotonin-secreting Raphe fibers normally **inhibit** the Bulboreticular Facilitatory area to produce sleep.In other words a center located below mid pontine level is required to cause sleep by inhibiting other parts of the brain

Injections of melatonin induce sleep.

Stimulation of the y-chiasmal Nucleus (SCN) of hypothalamus **by light** falling on the retina → inhibits Melatonin release from Pineal gland & produces wakefulness.

Melatonin as a Circadian Controller of Sleep-Wake Cycles:

- Alternating "Sleep-Wake Cycles" are under marked Circadian Control.
- "Circadian Control/Rhythm": is the regulation of a biological rhythm (e.g. sleep-wakefulness, hormone secretion , etc) by day- night cycles .
- Darkness/night stimulates the Pineal Gland to secrete melatonin hormone.
- Melatonin **inhibits** the RAS & thereby induces SWS.
- Daylight falling on the retina stimulates the Suprachiasmal Nucleus (SCN) of hypothalamus.
- **SCN** inhibits melatonin secretion by the Pineal Gland, & thereby it inhibits sleep and **promotes wakefulness.**

Sleep Disorder	Definition/About
Insomnia	Definition: habitual sleeplessness; inability to sleep. • Reported to affect approximately 25% of the population occasionally, and 9% regularly. • No single definition of insomnia. • One of the most important causes of insomnia is sleep medications. • Insomnia is not a disease, but rather may be a symptom of pain, discomfort or other physical ailment.
Drug dependency insomnia	An insomnia caused by the side effects of ever increasing doses of sleeping medications.
Sleep apnea	Cessation of breathing while sleeping (people who are overweight).
Somnolence	Extreme sleepiness
Narcolepsy	A sleep disorder characterized by periods of irresistible sleep, attacks of cataplexy, sleep paralysis, and hypnagogic hallucinations.**Orexin (also called hypocretin) is produced by neurons in the hypothalamus that provide excitatory input to many other areas of the brain.Orexin neurons are most active during waking and almost stop firing during slow wave and REM sleep.Loss of orexin signaling as a result of defective orexin receptors destruction of orexin-producing neurons causes narcolepsy**
Sleep attack	A symptom of narcolepsy; an irresistible urge to sleep during the day, after which the person awakes feeling refreshed.
Cataplexy	A symptom of narcolepsy; complete paralysis that occurs during waking.**Patients with narcolepsy may also experience a sudden loss of muscle tone (cataplexy)**
Sleep paralysis	A symptom of narcolepsy; paralysis occurring just before a person falls asleep.
Hypnagogic hallucination	A symptom of narcolepsy; vivid dreams that occur just before a person falls asleep; accompanied by sleep paralysis.
REM sleep behavior	A neurological disorder in which the person does not become paralyzed during REM sleep and thus acts out dreams.

Neural Control of Arousal	
Acetylcholine	• **One of the most important neurotransmitters involved in arousal.** • **Two groups of acetylcholinergic neurons are located in pons & basal forebrain**, produce activation & cortical desynchrony when they are stimulated.
Murmyl peptide	**induces sleep**
Norepinephrine	Catecholamine agonists produce arousal & sleeplessness effects appear to be mediated by the locus coeruleus in the dorsal pons.
Locus ceoruleus	A dark-colored group of noradrenergic cell bodies located in the pons near the rostral end of the floor of the fourth ventricle; involved in arousal and vigilance.
Serotonin (5-HT)	Appears to play a role in activating behavior; almost all of the brain's serotonergic neurons are found in the Raphe nucleus, located in the medullary and pontine regions of the brain.
Raphe nucleus	A group of nuclei located in the reticular formation of the medulla, pons & midbrain. Situated along the midline, contain serotonergic neurons.
Histamine	A neurotransmitter implicated in control of wakefulness and arousal; a compound synthesized from histidine, an amino acid.
Tuberomammillary nucleus	A nucleus in the ventral posterior hypothalamus, just rostral to the mammillary bodies; contains histaminergic neurons involved in cortical activation and behavioral arousal.
Neural Control of Slow-Wave Sleep	
Ventrolateral preoptic area (VLPA)	• A group of GABAergic neurons in the preoptic area whose activity suppresses alertness and behavioral arousal and promotes sleep. • Destruction of this area has been reporter to result in total insomnia, coma, and eventual death in rats.
Neural Control of REM sleep	
PGO wave (Pontine, Geniculate, Occipital)	Bursts of phasic electrical activity originating in the pons, followed by activity in the lateral geniculate nucleus and visual cortex, a characteristic of REM sleep.

The Executive Mechanism	
Peribrachial area	The region around the brachium conjunctivum, located in the dorsolateral pons; contains acetylcholinergic neurons involved in the initiation of REM sleep.
Carbachol	A drug that stimulates acetylcholine receptors.
Medial pontine reticular formation (MPRF)	A region that contains neurons involved in the initiation of REM sleep; activated by acetylcholinergic neurons of the peribrachial area.
Magnocellular nucleus	A nucleus in the medulla; involved in the atonia (muscular paralysis) that accompanies REM sleep.
Biological Clocks	
Suprachiasmatic nucleus	A nucleus situated atop the optic chiasm. It contains a biological clock responsible for organizing many of the body's circadian rhythms.
Melanopsin	A photopigment present in ganglion cells in the retina whose axons transmit information to the SCN, the thalamus, and the olivary pretectal nucleus.
Intergeniculate leaflet (IGL)	A part of the lateral geniculate nucleus that receives information from the retina and projects to the SCN; terminals release neuropeptide Y at the SCN.

❖ Quick review

- ★ **REM** a kind of sleep that occurs at neurons of the pons and is characterized by rapid eye movements, **more** dreaming and **faster** pulse and breathing. Dreams **can** be remembered
- ★ episodes of REM sleep lasting **5 to 30** minutes usually appear on the average every 90 minutes.
- ★ In **REM** Muscle tone throughout the body is exceedingly depressed **except** eye muscles
- ★ In **REM** the **brain is quite active** but is not aware & cut-off from the external world.

- ★ **NREM (SWS)** A stage where sleep EEG waves are generally of low frequency, and is not associated with rapid eye movements. Dreams **can't** be remembered, is more **restful** than REM

- ★ The difference between **sleep** and **coma** is the sleep **can** be aroused by appropriate sensory or other stimuli. While the coma **can't**

- ★ Alpha activity (waves) : Awake, but **non-attentive**, large, **regular**. Generally associated with a state of relaxation.
- ★ Beta activity (waves) :Awake and **attentive** - low amplitude, fast, **irregular**. generally associated with a state of arousal
- ★ **Physiological change** in sleep. It **decreases:** pulse rate, cardiac output, blood pressure, vasomotor tone, tidal volume, respiratory rate, BMR 10-15%, urine volume & salivary/lacrimal secretions). And **increases** *blood volume &* gastric/sweat secretions
- ★ Insomnia is habitual sleeplessness; inability to sleep.
- ★ Sleep Apnea is the cessation of breathing while sleeping (people who are overweight).

Questions

1. In a typical night of sleep for adults, there are about:
   A) 3-6 cycles
   B) 2-4 cycles
   C) 4-5 cycles
   D) 4-6 cycles

2. Which of the following statements about sleep is correct?
   A) Although fast-wave sleep is frequently referred to as “dreamless sleep,” dreams and sometimes nightmares do occur at this time
   B) Individuals rarely will awaken spontaneously from rapid eye movement (REM) sleep
   C) Muscle tone throughout the body is markedly depressed during REM sleep (except for eye muscles)
   D) Heart rate and respiratory rate typically become very regular during REM sleep

3. Beta waves indicate:
   A) Deep sleep
   B) Awake, non-attentive
   C) Awake, attentive
   D) REM

4. Which of the following statements concerning electroencephalogram activity is correct?
   A) Delta waves occur in normal adults who are awake but in a quiet, resting state
   B) Alpha waves occur at 14 to 80 cycles per second during periods of heightened excited activity or high tension
   C)Theta waves are associated with a state of arousal
   D) Delta waves occur during the deepest stages of SWS

5. The state of unconsciousness from which a person can not be aroused by any external stimuli, is known as:
   A)Awakeness
   B)Coma
   C)Sleep
   D)Death

6. As the person becomes more rested through the night, the duration of:
   A) SWS increases.
   B) REM decreases.
   C) REM remains the same.
   D) REM increases.

Answers:
1.D
2.C
3.C
4.D
5.B
6.D
7.B
8.D
9.D
10.B

7. REM sleep accupies …. of the total sleep of full-term neonates:

A) 25%
B) 50%
C) 80%
D) 15%

8. The cessation of breathing while sleeping is also known as:

A) Sleep attack
B) Cataplexy
C) Narcolepsy
D) Sleep apnea

9. Which property can be seen in Slow-wave sleep?

A) Impaired thermoregulation
B) Increased brain temperature
C) Rapid, coordinated eye movements
D) Reduced cerebral blood flow.

10. During SWS, **all** the body's secretions are reduced.

A) True
B) False

Answers:
1.D
2.C
3.C
4.D
5.B
6.D
7.B
8.D
9.D
10.B