Physiology of Sleep

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Objectives:

1. Explain the difference between **sleep** and **coma**.

2. Define **NREM** (non-rapid eye movement, SWS) and **REM** (rapid eye movement) sleep.

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

4. Describe the **behavioral** and **autonomic** features associated with **NREM** and **REM** sleep.

5. Describe **EEG**, as a **physiological tool**, is being used to delineate in which stage of sleep (or wakefulness) a person is.

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

7. Describe the **current theories** about the neural basis of sleep.

WHAT IS SLEEP?

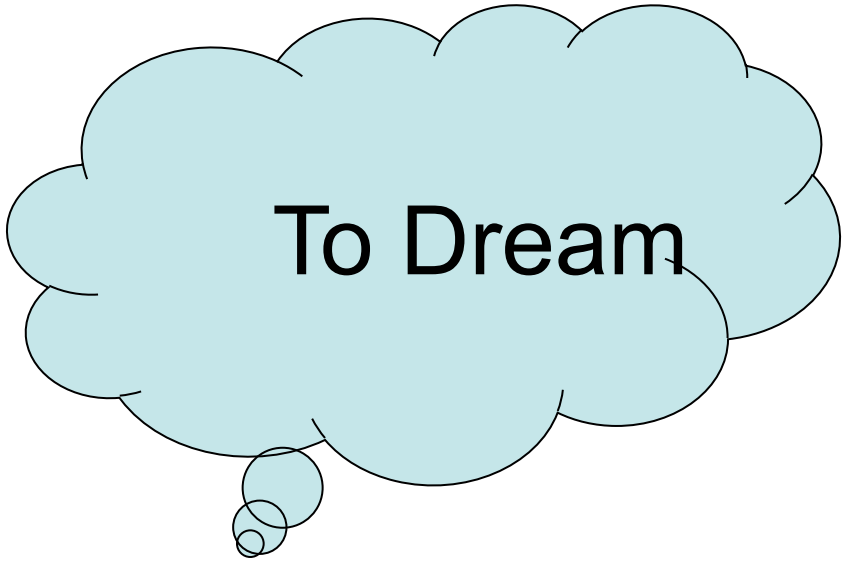
Sleep: State of unconsciousness from which a subject can be aroused by appropriate sensory or other stimuli.

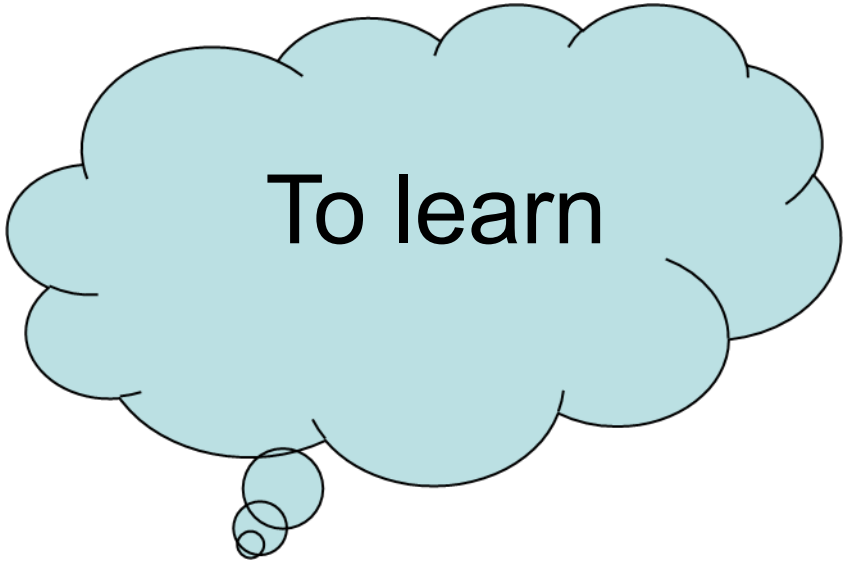
- Sleep may also be defined as a normal, periodic, inhibition of the reticular Activating system.

***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?





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 we 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?

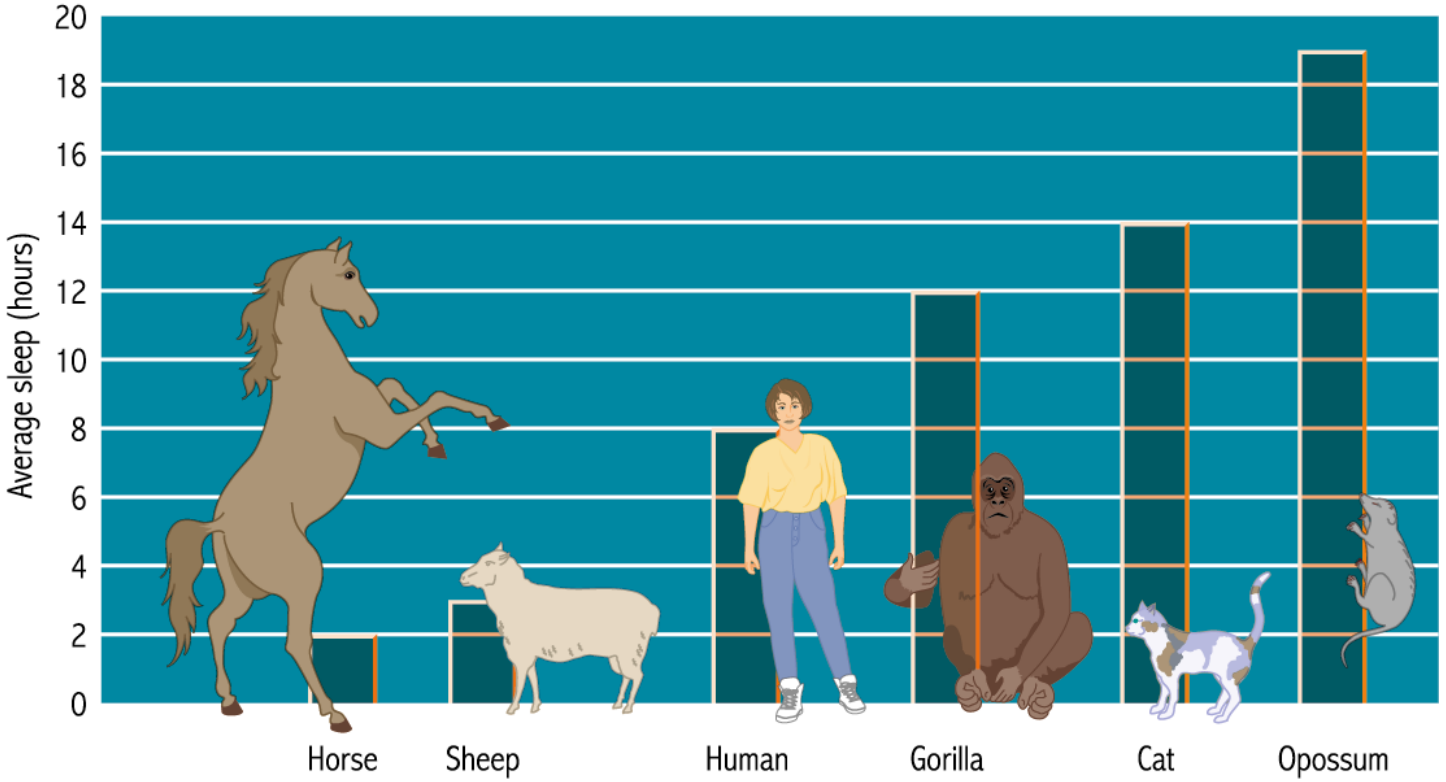
Why Do We Sleep?

Explanation

- **Proximate:**
  - Feeling tired (melatonin ↑).
  - consolidate energy & experiences.
  - restore body cells &promote protein anabolism.
  - Maintain hormonal secretions, immune function.
  - avoid predators.

- **Ultimate:**

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


Average sleep (hours)
20
18
16
14
12
10
8
6
4
2
0
Horse
Sheep
Human
Gorilla
Cat
Opossum

Stages of Sleep: recorded by EEG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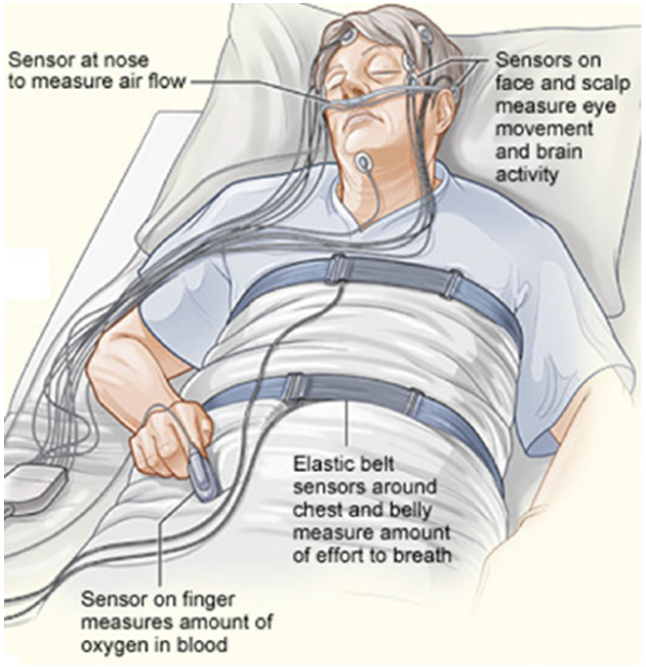
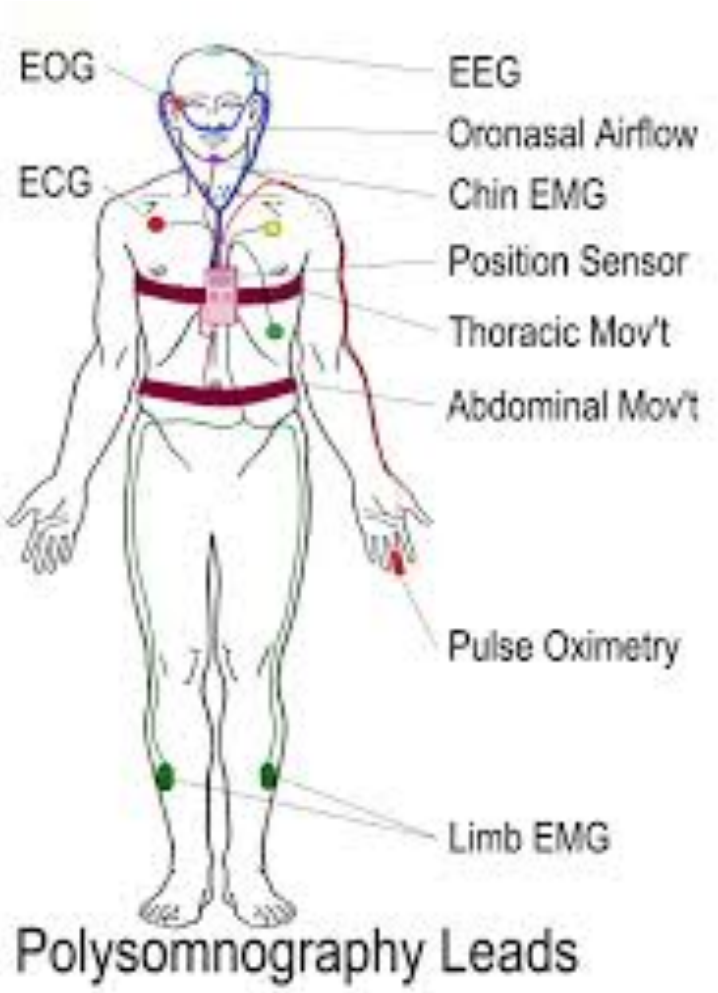

Sensor at nose to measure air flow
Sensors on face and scalp measure eye movement and brain activity
Elastic belt sensors around chest and belly measure amount of effort to breath
Sensor on finger measures amount of oxygen in blood


EOG
ECG
EEG
Oronasal Airflow
Chin EMG
Position Sensor
Thoracic Mov't
Abdominal Mov't
Pulse Oximetry
Limb EMG
Polysomnography Leads

Sleep Classification

NREM (non-rapid eye movement) (SWS) slow wave Sleep

REM (rapid eye movement) Sleep

Sleep is promoted by a complex set of *neural* & *chemical* mechanisms:

Daily rhythm of sleep & arousal: suprachiasmatic nucleus of the hypothalamus pineal gland's secretion of melatonin.

(1) SWS (Slow-Wave Sleep),

- this type of sleep, EEG waves are generally of low frequency .
- Non-Rapid Eye Movement (NREM) sleep because , unlike the other type of sleep , it is not associated with rapid eye movements .

- **Raphe nuclei of the medulla & pons and the secretion of serotonin.**

(2) REM sleep (Rapid Eye Movement)

- this type of sleep rapid eye movements occur (**Neurons of the pons)**

Sleep Classification Based on EEG Features

NREM Sleep (SWS)

4 stages:

- **Stage 1 → when a person is initially falling asleep . *Alpha* waves diminish &Theta waves appear on EEG.**

- **Stage 2 → This is the first stage of true sleep.**

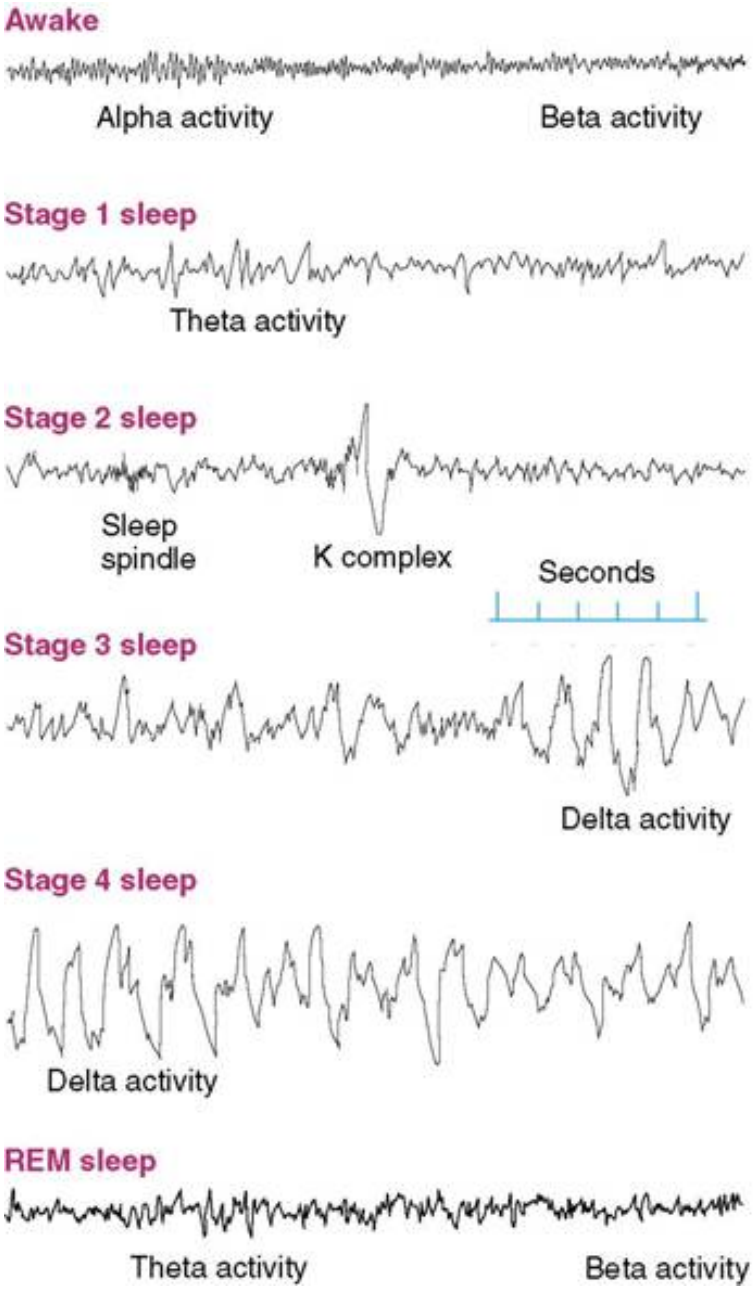
  Marked by appearance of *Sleep Spindles* . These are bursts of alpha-like 10-14 z, 50 uV waves .

- **Stage 3 → Lower frequency (mainly theta), higher amplitude EEG waves. Body temperature begin to fall. BP decreases. Difficult to awaken the person. This stage occurs about 20-25 min after falling asleep.**

- **Stage 4 → Still slower frequency (mainly delta) & still higher amplitude waves . The difference is that the dreams in SWS are not remembered but in REM, dreams can be remembered.**

REM Sleep

- **Low-voltage, fast activity.**



Alpha activity:

smooth electrical activity of 8–12 Hz, generally associated with a state of relaxation.

Beta activity:

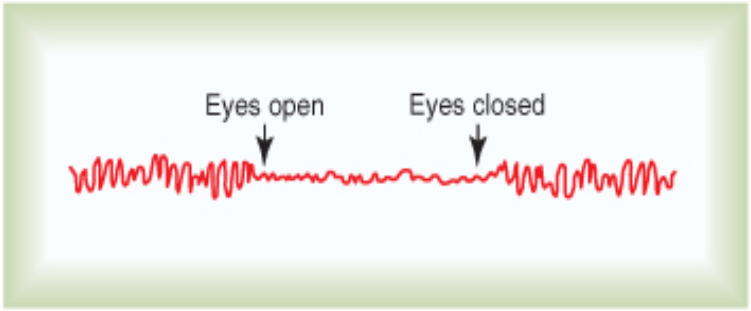
Irregular electrical activity of 13–30 Hz, generally associated with a state of arousal.

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.



Distribution of Sleep Stages

- **SWS occupies most of the total**

night sleep time (around 75-80%), it is interrupted by intervening REM sleep periods, ≅ every 90 minutes .

- **In a typical night of sleep, a young**

adult (1) first enters NREM sleep, passes through stages 1 , 2 , 3 &4 SWS, then, 60-100 min from sleep onset, goes into t first REM sleep episode.

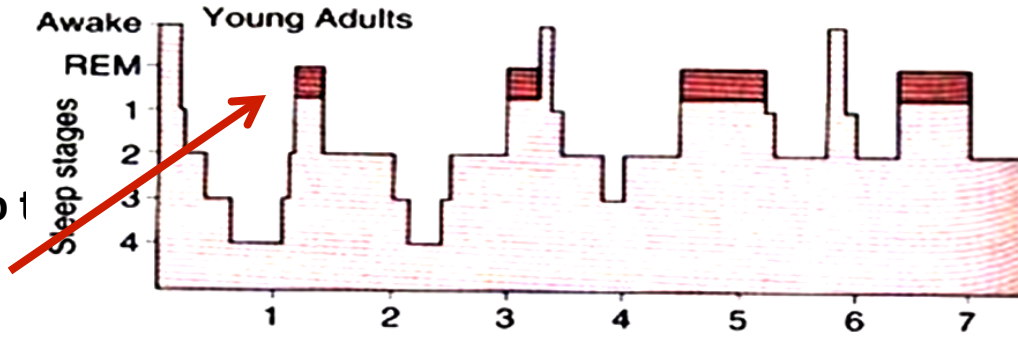
- **This cycle is repeated at intervals of**

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 periods are shown in red

In young adults SWS (NREM sleep) occupies 75-80% of night sleep time & REM sleep occupies 20-25 % of the sleep time.

REM Sleep (Paradoxical Sleep)

- **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, each episode of REM sleep is short, and it may even be absent.**

- **Conversely, as the person becomes more rested through the night, the durations of the REM episodes increase.**

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

(1) There are rapid eye movements .

(2) Muscle tone throughout the body (except eye muscles) is exceedingly depressed .

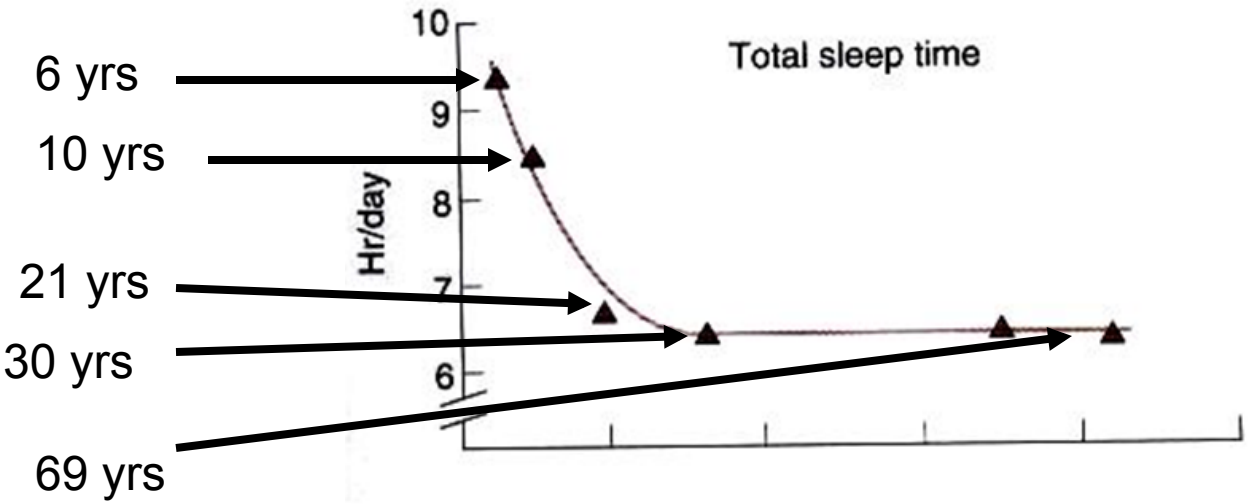
REM Sleep (Paradoxical Sleep) *cont..*

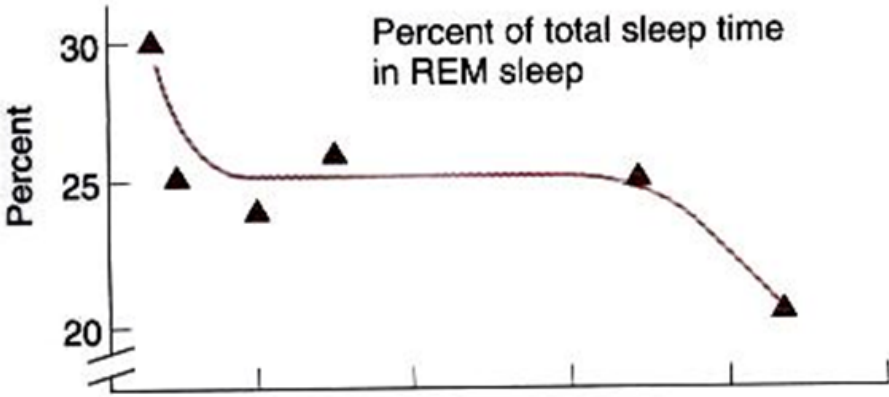
•REM sleep is a type of sleep in which the brain is quite active, but this brain →

(1)is not aware cut-off the external world.

(2) its activity is not channeled into purposeful external motor activity.

New born = 15 - 20 hours.
Children = 10 -15 hours.
Adults = 6-9 hours.
Old age = 5-6 hours.





- REM sleep occupies 80% of total sleep time in premature infants & 50% in full-term neonates.
- Thereafter, the proportion of REM sleep falls rapidly and plateaus at about 25% until it falls further in old age .
- Children have more total sleep time & stage 4 sleep than adults.

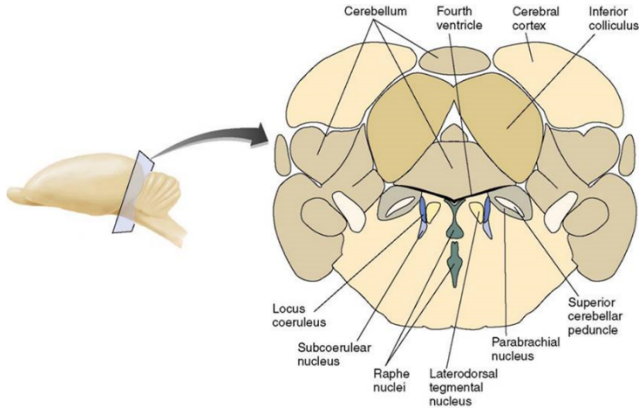
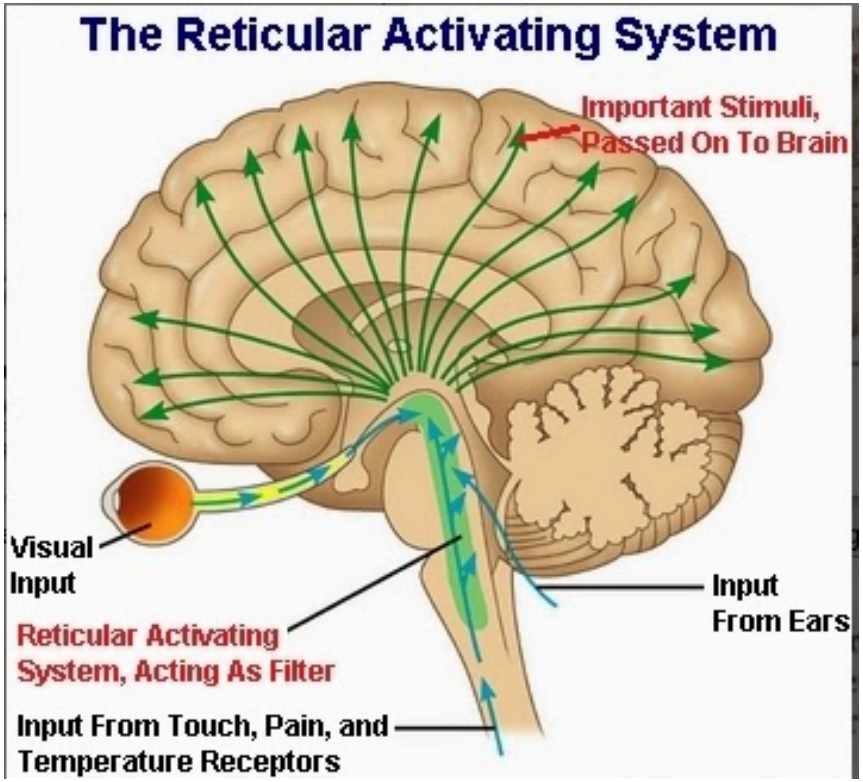
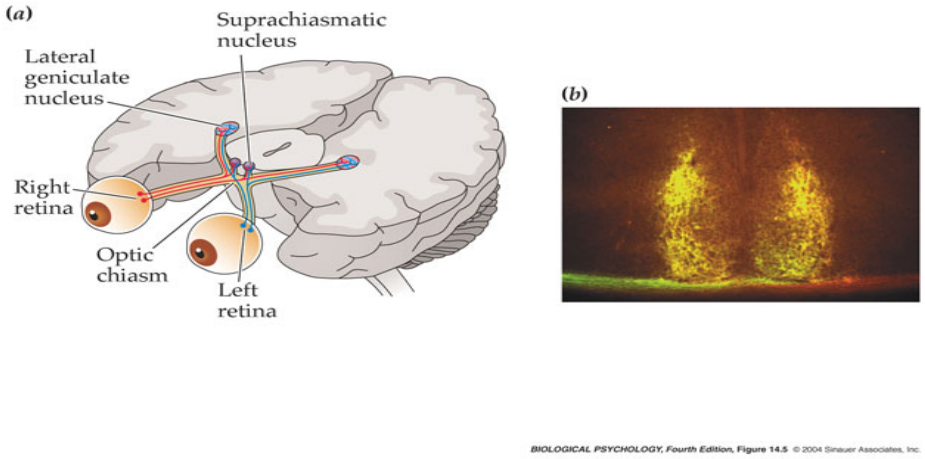


TABLE 14.2 ***Neural Activity of Neurotransmitter Systems during Sleep and Arousal***

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.

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.

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

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:**

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

{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 Facilitory area of the RAS].

Indication that the serotonin-secreting Raphe fibers normally **inhibit** the Bulboreticular Facilitory area to produce sleep.

Injections of melatonin induce sleep.
Stimulation of the Supra-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 DISORDERS /BURDEN

70 million people in the US suffer from sleep problems [50% have chronic sleep disorder]

Insomnia = 30 million
sleep apnea= 18 million
Narcolepsy= 250,000 Americans have
Motor Car Accidents= 100,000
traffic fatalities =1500 drowsy driving/annum

Approximately $16 billion annually the cost of healthcare in USA & result in $50 billion annually in lost productivity.

- **Disorders of Sleep:**
  - Insomnia (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.

- **Narcolepsy:**
  - A sleep disorder characterized by periods of irresistible sleep, attacks of cataplexy, sleep paralysis, and hypnagogic hallucinations.
- **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.
- **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 Behavior Disorder

– REM sleep behavior:

- A neurological disorder in which the person does not become paralyzed during REM sleep and thus acts out dreams.

❑Physiological Mechanisms of Sleep & Waking:

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.

❑Physiological Mechanisms of Sleep & Waking:

Neural Control of Arousal

- 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.

- Physiological Mechanisms of Sleep & Waking:

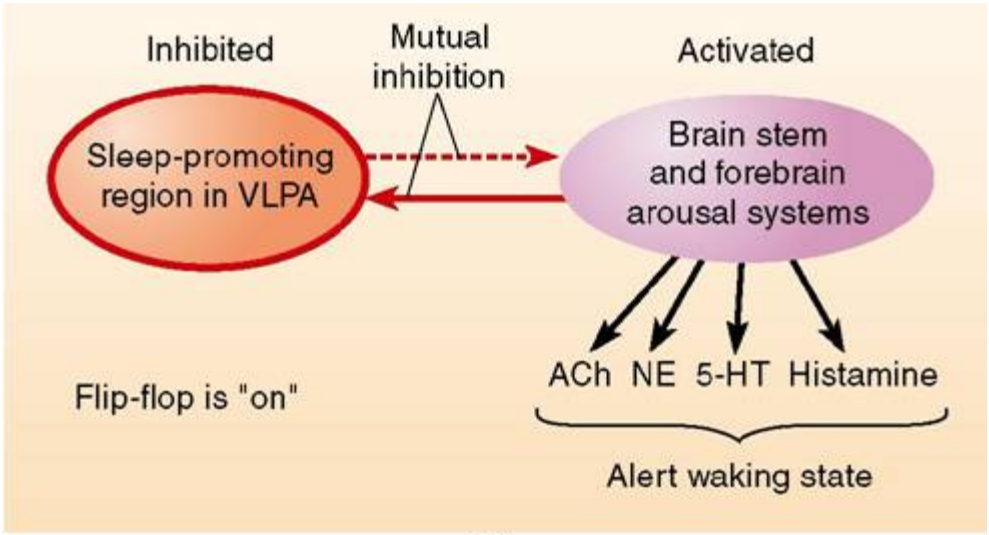
Neural Control of Arousal

–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.



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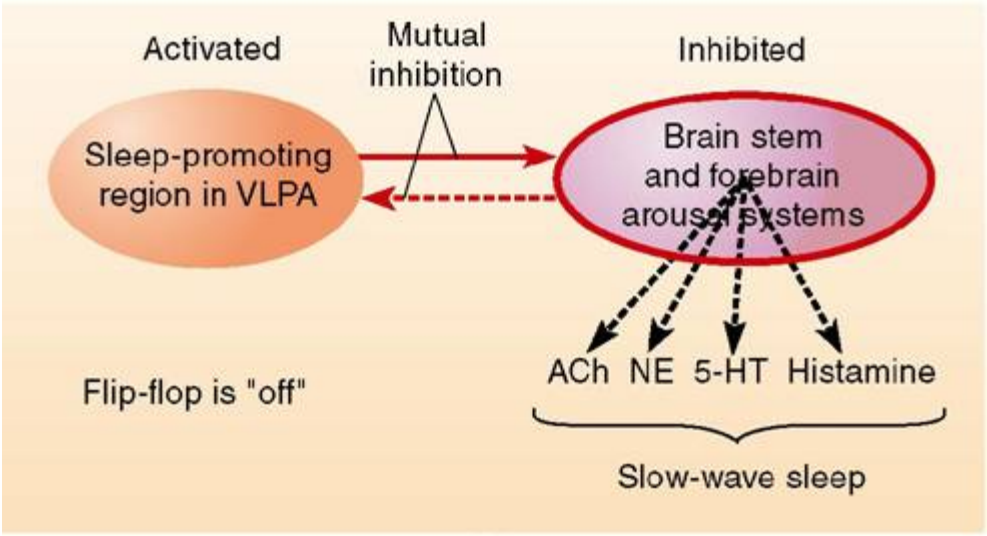

(b)

Physiological Mechanisms of Sleep and Waking

- Neural Control of Arousal

- 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.

Physiological Mechanisms of Sleep and Waking

- Neural Control of Arousal

- Hypocretin:
  - A peptide also known as orexin, produced by neurons whose cell bodies are located in the hypothalamus; their destruction causes narcolepsy.

Physiological Mechanisms of Sleep and Waking

- 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.

Physiological Mechanisms of Sleep and Waking

- 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.

Physiological Mechanisms of Sleep and Waking

- 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.

Physiological Mechanisms of Sleep and Waking

- The Executive Mechanism

- 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

- The Suprachiasmatic 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.

Biological Clocks

- The Suprachiasmatic Nucleus

- 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.


Good night …
Sleep tight …