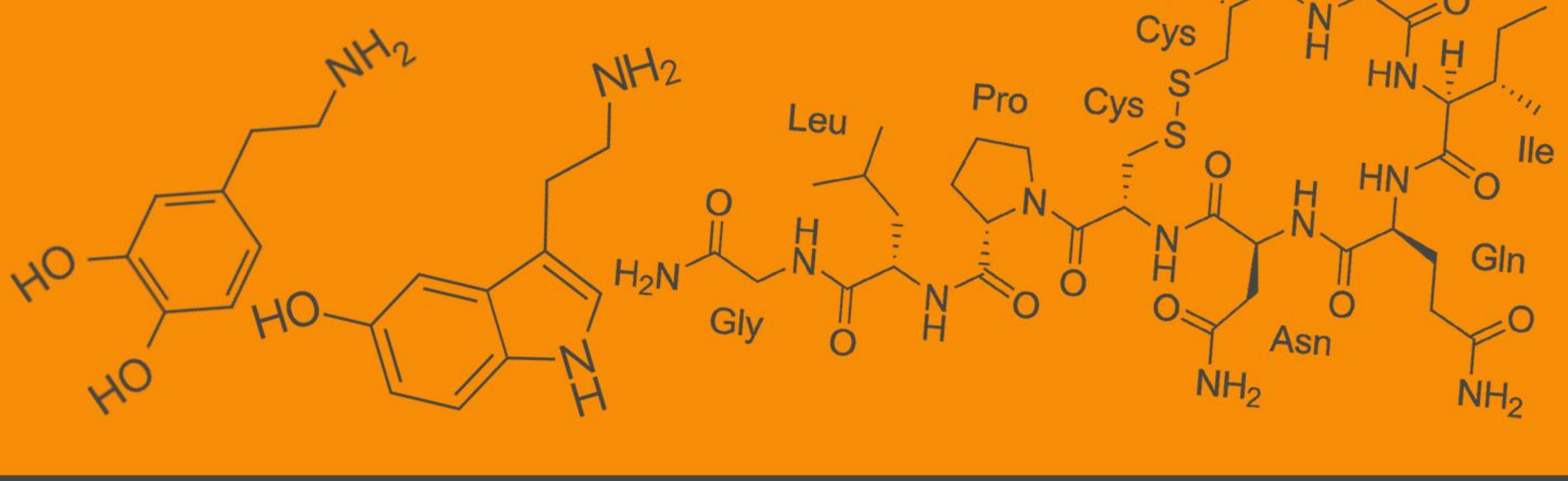


MEDICINE438's CNSPHYSIOLOGY

LECTURE VII: Physiology of Sleep

EDITING FILE GSLIDES

IMPORTANT MALE SLIDES EXTRA FEMALE SLIDES LECTURER'S NOTES

1 Physiology of Sleep

Lecture Seven

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.

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. OR A normal, periodic, inhibition of the reticular Activating system.
Wakefulness	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.

Table 7-1

INTRODUCTION: Why Do We Sleep?

SLEEP THEORY #1	SLEEP THEORY #2	SLEEP THEORY #3	SLEEP THEORY #4
TO REST	**TO HEAL**	**TO LEARN**	**TO DREAM**
To gain relief from this hyperactive state.	Sleep also allows us to heal our bodies. The immune system (refer to BOX 7-1) (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 may help the human brain get better organized - by filing away important memories and discarding unwanted information.	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 GOAL Sustains our ability to reproduce successfully, by maintaining good health.

PRESENT ONLY IN FEMALE SLIDES

SLEEP HAS BEEN POSTULATED TO SERVE MANY FUNCTIONS

1. Neural maturation
2. Facilitation of Memory or Learning
3. Cognition
4. Clearance of Metabolic Waste Products Generated By Neural Activity in the Awake Brain
5. Conservation of Metabolic Energy
6. Restore of Natural Balances among the Neuronal Centers

BOX 7-1: CLINICAL RELEVANCE

It was shown in a recent study published in Journal of Experimental Medicine, that sleep induces the activation of cell-adhesion molecules, called **integrins** by T-cells.

- T-cells arise from lymphoid precursor cells (stem cell capable of differentiation into many lymphocyte varieties), then they undergo maturation in the thymus where they are selected based on their ability to bind antigens and their ability to discriminate between self and non-self antigens (a novel mechanism in which stromal cells in the thymus showcase present antigens in distant organs, like abdominal, to test maturing T-cells within the thymus), The few T-cells that survive the maturation process migrate between secondary lymphoid organs, such as lymph nodes, by the help of those **integrins** as naive T-cells, remember T-cells can not recognize antigens by themselves, they await antigen-presenting cells to activate them by presenting antigens in a digestible form that can be recognised by T-cells. (as peptides in association with MHC-1 or MHC-2). These processes involve **integrins** which are proven to be helpful in T-cell motility and subsequent function.

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

SLEEP IS CAUSED BY AN ACTIVE INHIBITORY PROCESS (BOX 7-2)

- **EARLY THEORY OF SLEEP**

The excitatory areas of the upper brain stem, the reticular activating system, simply became fatigue during the day activities, waking day and became inactive as a result.

- **CURRENT THEORY**

Sleep is caused by an ***active inhibitory process.***

SLEEP CENTERS

Normal sleep is under control of the reticular activating system in the upper brain stem and diencephalon.

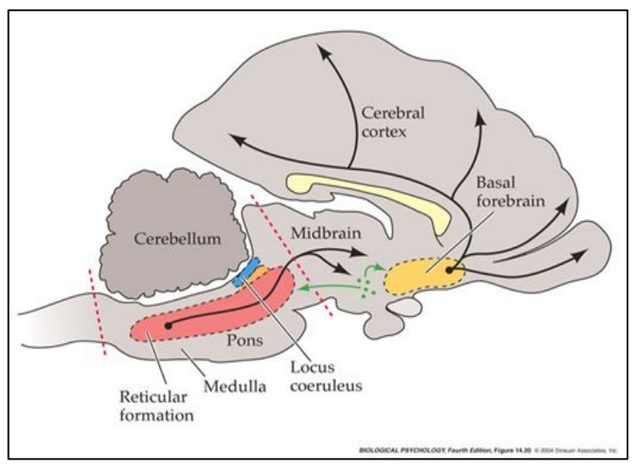


Figure 7-1

HUMAN SLEEP DURATION

NEW BORN	15-20 hours.
CHILDREN	10-15 hours.
ADULT	6-9 hours.
OLD AGE	5-6 hours

Table 7-2

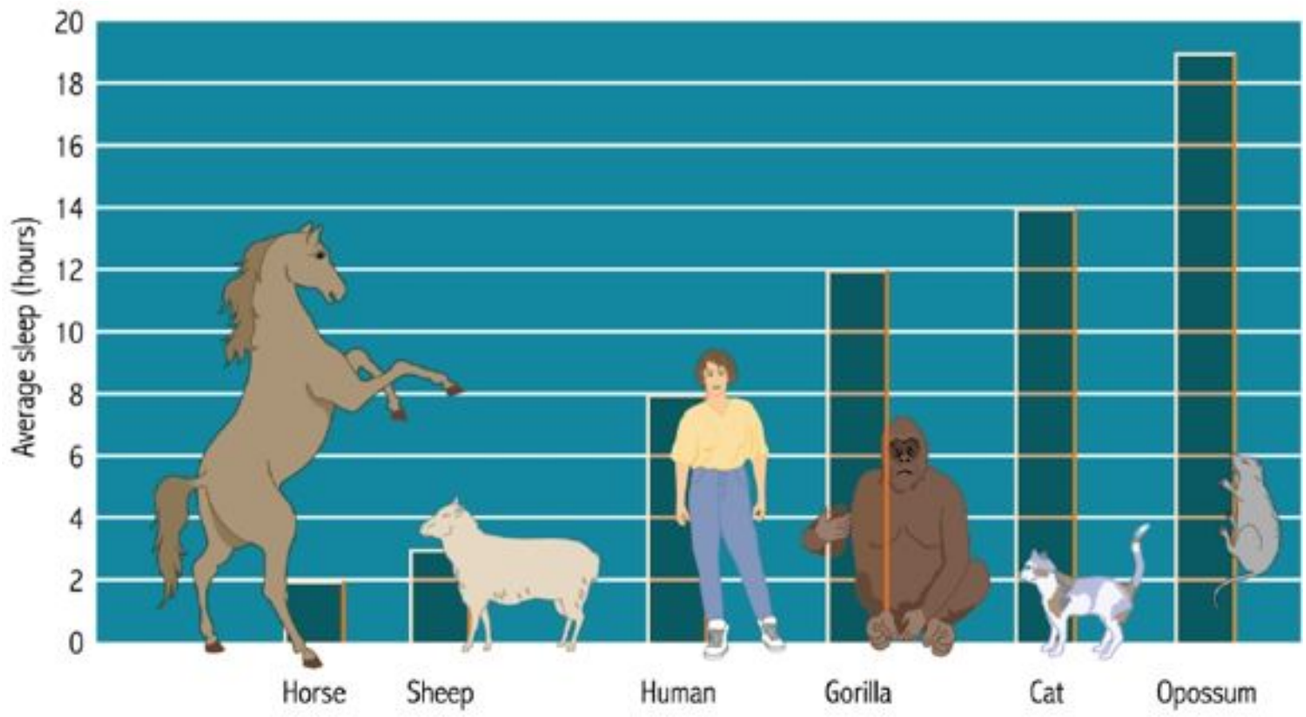


Figure 7-2

BOX 7-2: GUYTON AND HALL

The reticular activating system is composed of scattered matrix of nerve cells and fibers that extend throughout the length of the brainstem.

- RAS activates the cerebral cortex, the conscious level of the CNS, and the bank of its memories, throughout several excitatory nuclei present in RAS, specifically in upper brainstem, that extend to the thalamus and through thalamocortical pathways, RAS can activate the cortex to resume consciousness.
- It was previously thought that sleep is caused by mere fatigue of this system during wakefulness, therefore resulting in stoppage of activating signals and initiation of sleep, however, an important experiment changed this notion.
- It was found in an experiment that by transecting the brainstem at the level of midpons, creates a brain whose cortex never goes to sleep, even though theoretically based on the old model, fatigue should occur. This suggested that an area located below midpons (where the transection occurred) must be involved in initiation of sleep, and that it was initiated by an inhibitory process. Raphe nuclei, whose fibers secrete serotonin is involved in this process. As well as NTS.

PHYSIOLOGICAL MECHANISMS OF SLEEP

- Stimulation of some specific areas of the brain can produce sleep.
- ***Raphe nuclei*** in the Medulla Oblongata: Fibers from these raphe neurons secrete ***serotonin.***
- Drugs that blocks the formation of ***serotonin*** administered to an animal, the animal cannot sleep for the next several days.
- ***Serotonin is associated with the production of sleep.***

SLEEP MECHANISM

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

- Daily rhythm of sleep and arousal ***suprachiasmatic nucleus*** of the ***hypothalamus***. (BOX 7-3)
- ***Pineal gland's*** secretion of ***melatonin*** (Increased melatonin to make sleepy).
- **Slow-wave sleep:** Raphe nuclei of the medulla and pons, the secretion of serotonin associated with initiation of sleep.
- **REM sleep:** Neurons of the pons.

Consists of two parts:

1. Mesencephalic part:

- Composed of area of grey matter of midbrain and pons. when this area is stimulated, nerve impulses going to thalamus and disperse to the cerebral cortex.
- This greatly affects the cortical activity.
- Mesencephalic part causes consciousness.

2. Thalamic part:

- Consists of gray matter in the thalamus. When the thalamic part is stimulated, it develop activity in the cerebral cortex.
- Thalamic part causes arousal that is awakening from deep sleep [sensory input, pain, light].
- The ***RAS and cerebral cortex continue to activate each other through a feedback system.***
- The RAS also has a feedback system with the spinal cord.

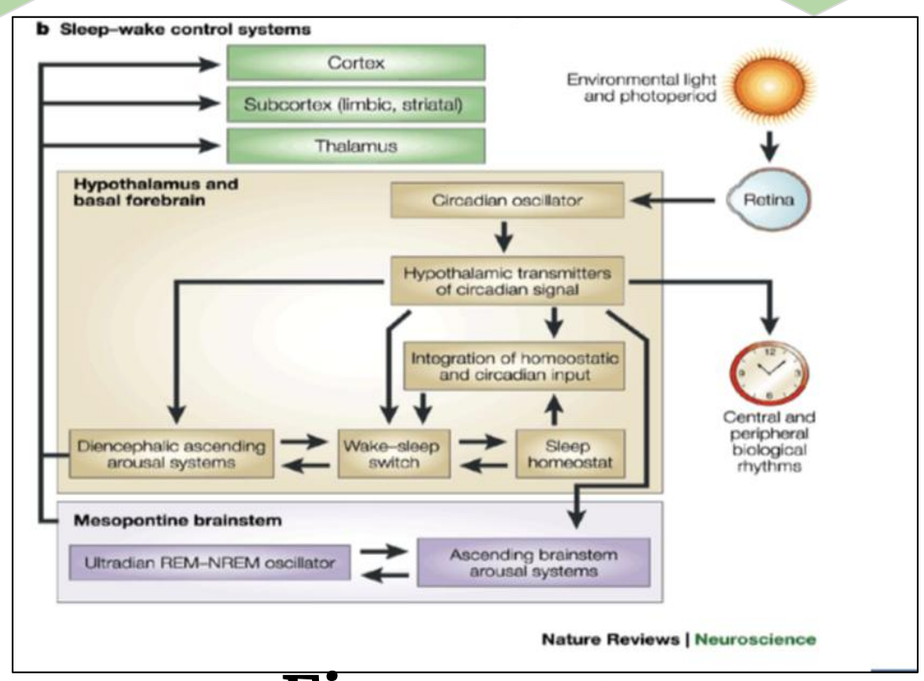
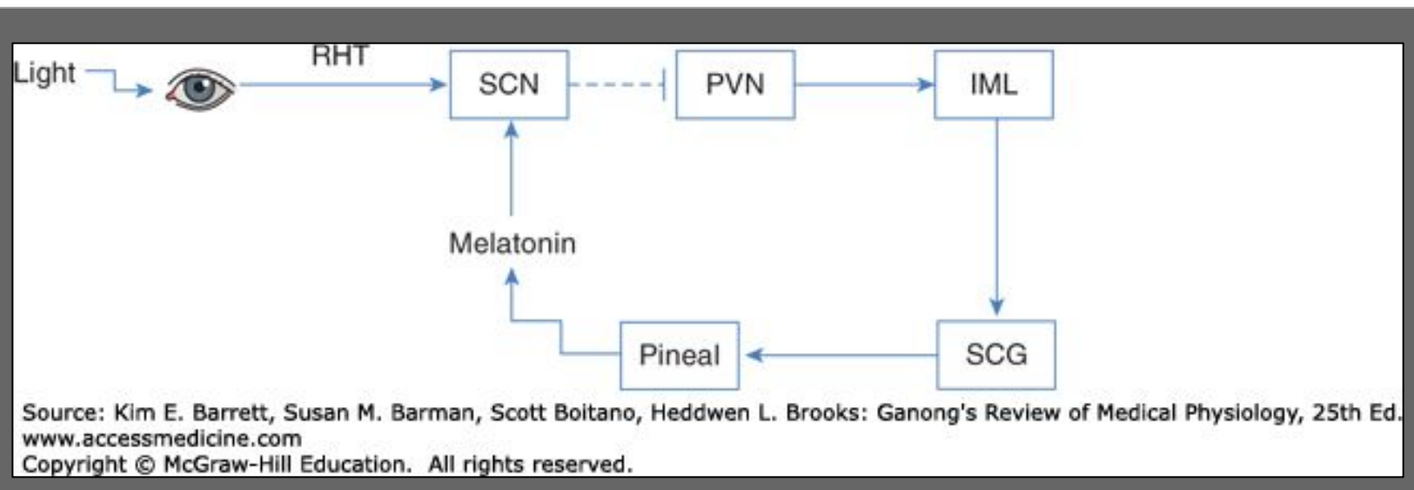


Figure 7-3

BOX 7-3: GANONG'S REVIEW OF MEDICAL PHYSIOLOGY



Suprachiasmatic nucleus of hypothalamus regulates this sleep and arousal rhythm by the process shown in the figure, light activates the SupraChiasmatic Nucleus (SCN), through the retina, SCN inhibits the ParaVertebral Nucleus (PVN) which stimulates melatonin release (sleep hormone) through a biochemical cascade. Therefore with less light, there will be less activation of SCN, and more melatonin release.

EEG IS USED TO DELINEATE WHICH STAGE OF SLEEP (OR WAKEFULNESS)

Sleep Classification is Based on EEG Features

Non-Rapid Eye Movement (NREM)				
	Stage 1	Stage 2	Stage 3	Stage 4
Experience	Falling asleep and transition stage between sleep and & waking	Baseline of sleep this is **the first step of true sleep**	**Deep sleep**	
Duration	1-5 mins (1-7 mins) ~ 2.5% of normal night sleep.	90 mins ~ 45-60% of normal night sleep.	15-30 mins ~ 40% of all sleep.	
Signs	Eyes begin to roll slightly. Feels relaxed with eyes closed.	-	Slowing heart rate, Breathing rate, and brain activity. Body temperature begin to fall. BP decreases. Difficulty awakening the person.	
Waveform	**Irregular, jagged, low-voltage wave.** **α & θ** waves appear on EEG. **α waves** diminish & **θ waves** appear	Sleep spindles: bursts of alpha-like 10-14 Hz, 50 uV waves. K-complex. sleep spindles (sudden, sharply, pointed waves 12-14-Hz (cycles/sec)	This stage occurs about 20-25 min after falling asleep. Lower frequency (mainly theta). Higher amplitude EEG waves. mixture of sleep spindles and delta waves	Still lower frequency (mainly delta). Higher amplitude waves.
Notes	Start when sleep has just begun. Brain activity starts to **decline**. Relaxed & closed eyes. Tells he's not been asleep, if have been awakened.	The person experiences only light sleep. It is a little harder to awake the person. Fragment of dream may be experienced. Eyes may slowly roll from side to side.	As the night goes on, there is progressive reduction in stage 3 and 4 & progressive increase in REM	

Table 7-3

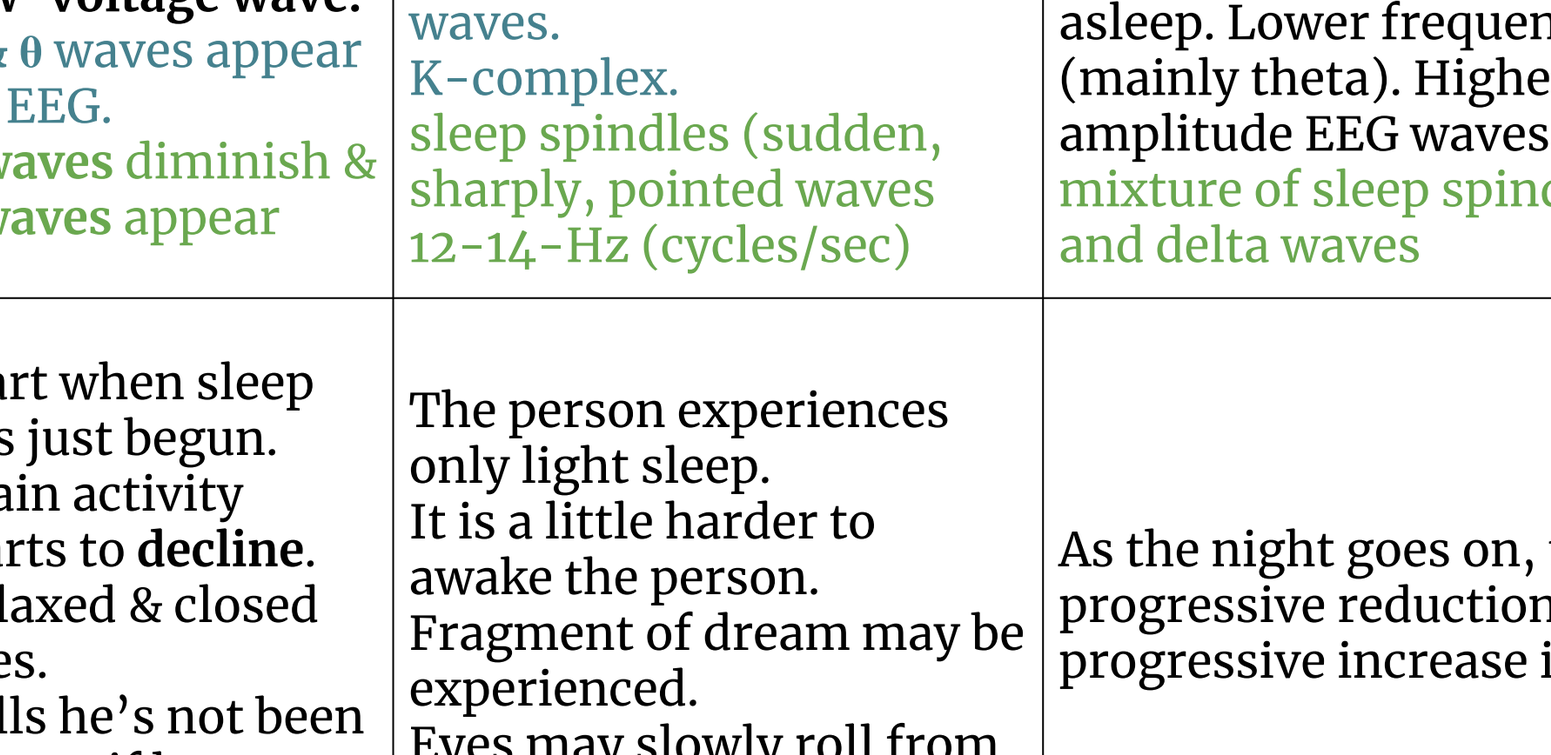


Figure 7-4

How Nrem And Rem Sleep Are Distributed During A Normal Night Sleep In The Average Adult Human

Distribution of Sleep Stages: Slow Wave Sleep occupies most of the total night sleep time (around 75-80%), it is interrupted by intervening Rapid Eye Movement 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 intervention to 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.

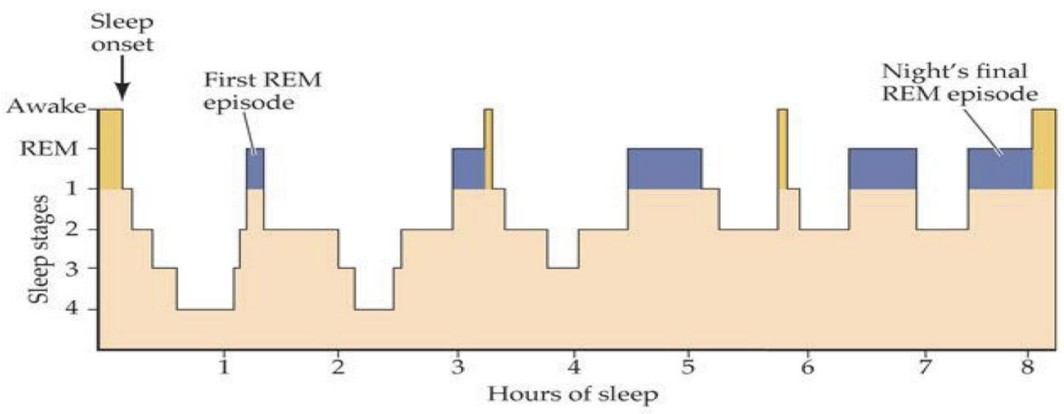


Figure 7-5

DESCRIBE THE BEHAVIORAL AND AUTONOMIC FEATURES ASSOCIATED WITH NREM AND REM SLEEP

Physiological Changes In Sleep
(These are the overall changes during slow-wave sleep, REM sleep can be different)

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 (**Basal metabolic rate** is the amount of energy expended while at rest) is decreased 10-15%.
Urine volume	**decreased**.
Secretions	Salivary/lacrimal secretions are **reduced**, gastric/sweat secretions are **increased**
Muscles	**Relaxed**
Reflexes	1. Superficial: unchanged except **plantex reflex.** 2. Deep: **reduced**

Table 7-4

Cont.

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

Figure 7-6[1]

EFFECTS PRODUCED BY AWAKENING AFTER 60-100 HOURS

- Equilibrium disturbed.
- Neuromuscular junction fatigue.
- Threshold for pain is lowered.
- Some cells shrink.

EEG Used To Delineate Which Stage Of Sleep (Or Wakefulness)

Electroencephalogram waves		
Alpha activity	**Smooth** electrical activity of 8-12 Hz.	Generally associated with state of **relaxation**.
Beta activity	**Irregular** electrical activity of 13-30 Hz.	Generally associated with state of **arousal.**
Theta activity	EEG activity of 3.5-7.5 Hz.	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.

Table 7-5

FOOTNOTES

1. All of them are important but Dr. Nirvana focused on the red boxes.

Cont.

EEG WAVES In wakefulness

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

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

Figure 7-7

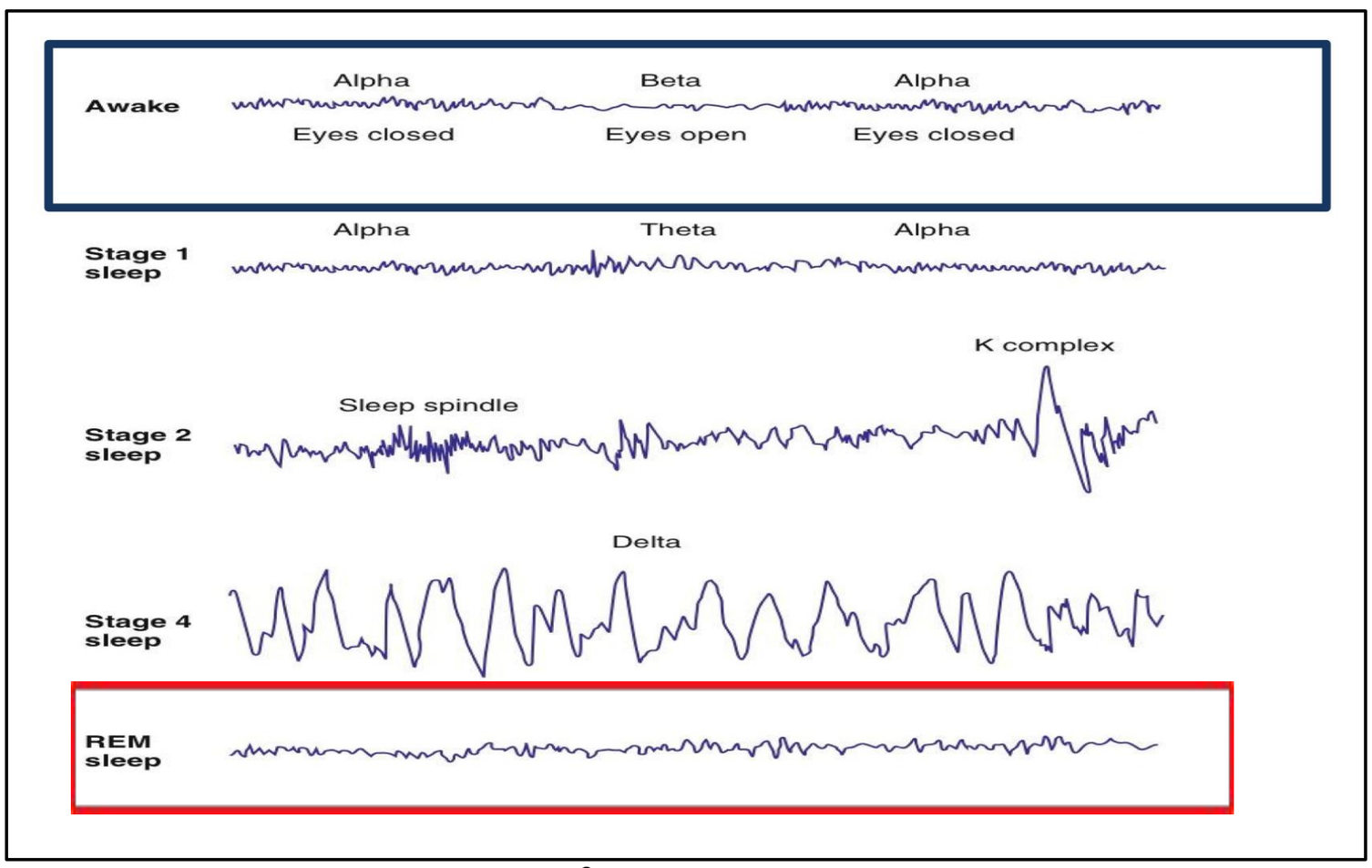


Figure 7-8

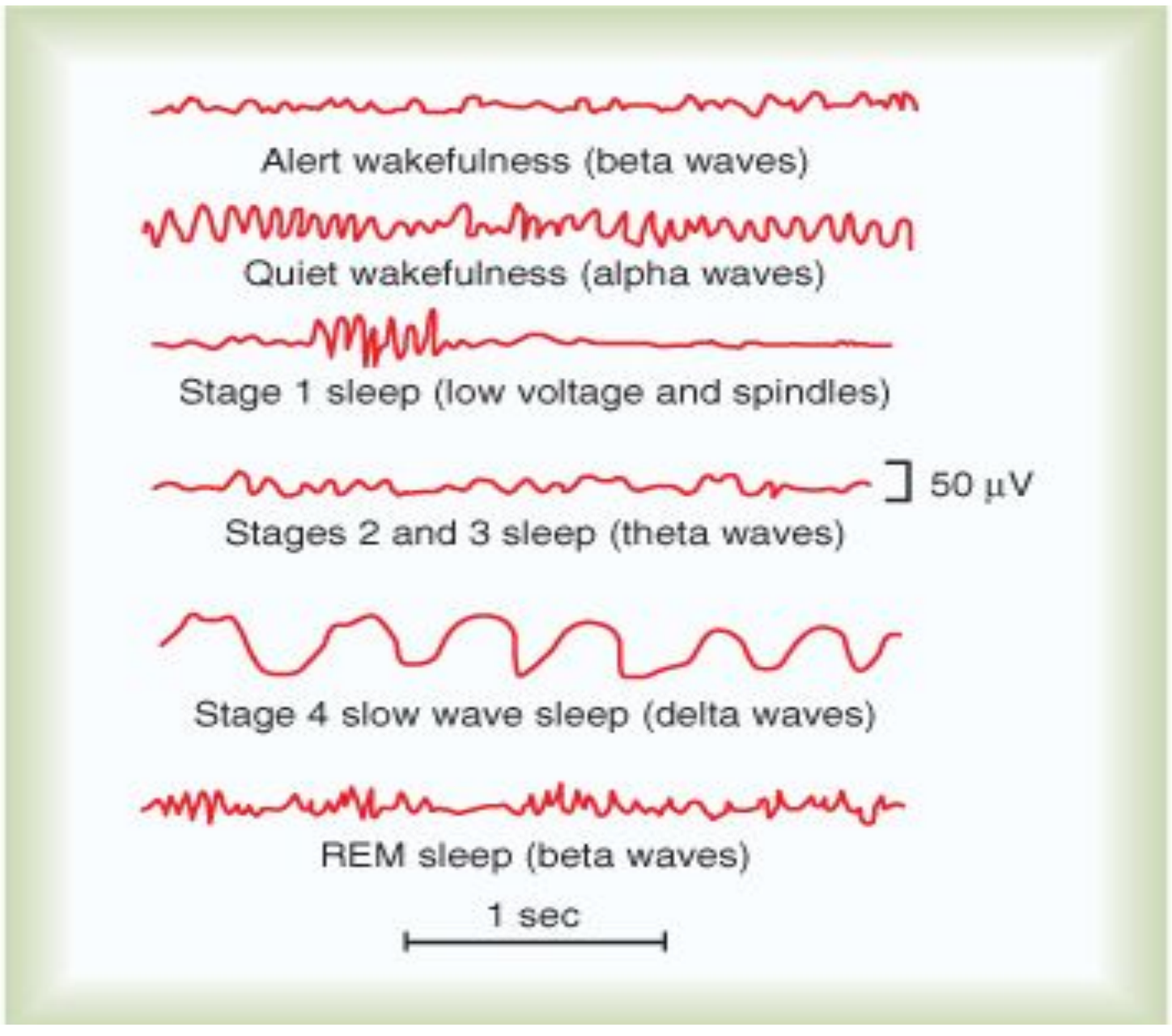


Figure 7-9

BOX 7-4: CLINICAL RELEVANCE

What Is Meant By Brain Waves?

In the brain, different regions of the brain contain different concentrations of ions carrying different charges, and concentrations change depending on brain activity, activated neurons are depolarized and hence, are positive inside, while hyperpolarized neurons are inactive, and hence are negative inside, generally.

- Large adjacent regions of the brain can be activated at the same time while others can be inhibited, this creates a voltage difference within the brain. Where an area will be more positive (containing more positive ions) than another area, this causes the movement of electrons towards the positive side from any less-positive side within the brain, thus producing an electric current. Producing an electric current generates a magnetic field, therefore we call brain waves "electromagnetic waves", it was found that at different states of wakefulness different regions are stimulated, therefore different regions contain different ions, as a result, ions will move in different directions and will show different brain waves, all due to ion movements. However, this still isn't perfect, since some brain waves can still be seen in sleep and wakefulness, even though the state of consciousness differ.

EEG is used to delineate which stage of sleep (or wakefulness):

Sleep Classification is Based on EEG Features

Rapid Eye Movement (REM)	
Experience	Very active stage of dream. Vocoders dreams can occur.
Duration	20-25% of normal night sleep.
Waveform	Irregular, low-voltage and fast activity. ***Beta waves.***
Notes	• Length of REM stages increases as the night progress "the duration of REM increases every cycle during long night sleep". • Heart rate & respiration become irregular. • In normal sleep bouts of REM sleep lasting for **5-30** minutes usually appear on the average after every **90 minutes.** • The **first** such period occurring **80-100** minutes after the person falls asleep • 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.*** • Muscle tone throughout the body (except eye muscles) is exceedingly depressed. • ***REM*** sleep is a type of sleep in which the brain is ***quite active***, but it is not aware "cut-off the external world" and its activity is not channeled into purposeful external motor activity. • **THE DREAMS IN SWS ARE NOT REMEMBERED, HOWEVER, THEY ARE REMEMBERED IN REM.** • **Drugs that mimic the action of acetylcholine increase the occurrence of REM sleep.** • **It has been postulated that the large acetylcholine secreting neurons in the upper brain stem reticular formation might, through their extensive efferent fibers, activate brain. This mechanism theoretically could cause excess activity of certain brain resigns in REM sleep.**

Table 7-6

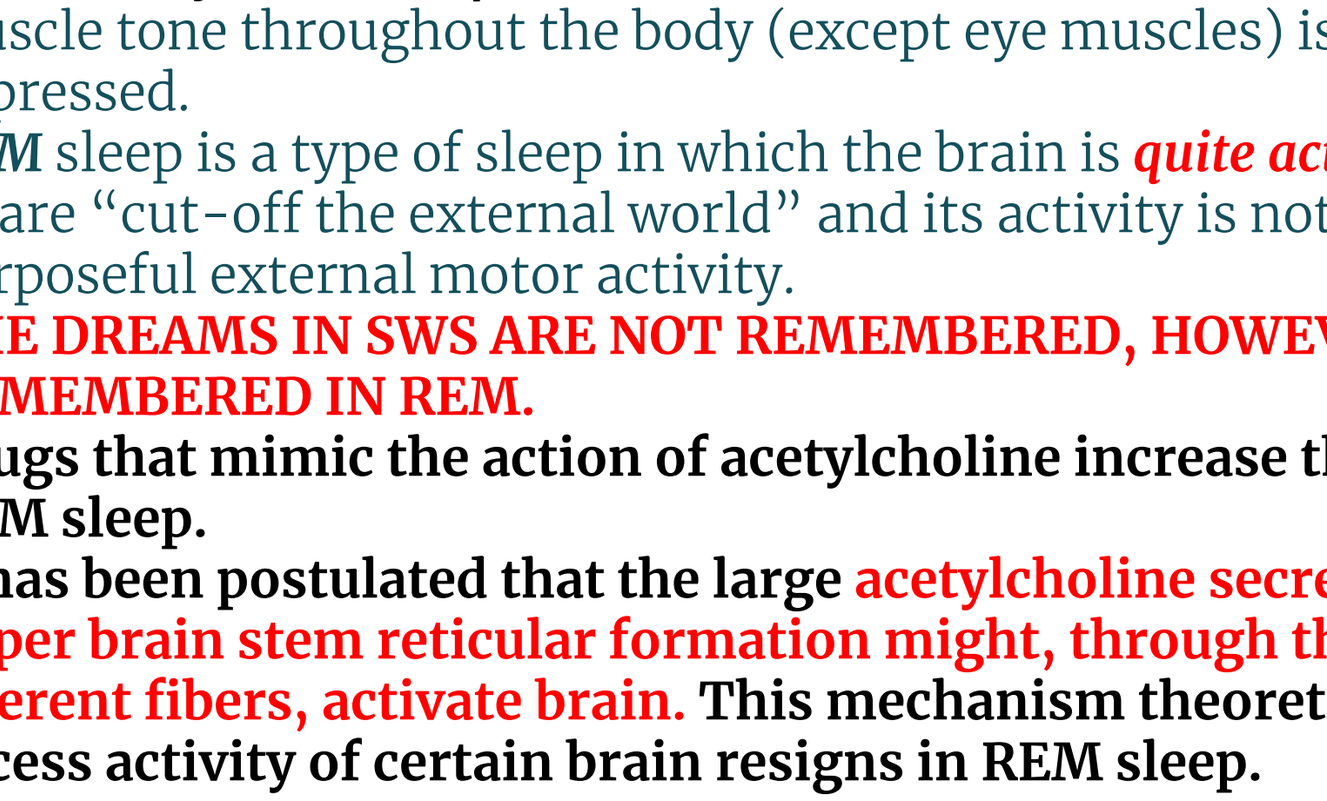


Figure 7-10

Total Sleep Duration And Different Sleep Stages Vary With Different Ages In Normal Humans

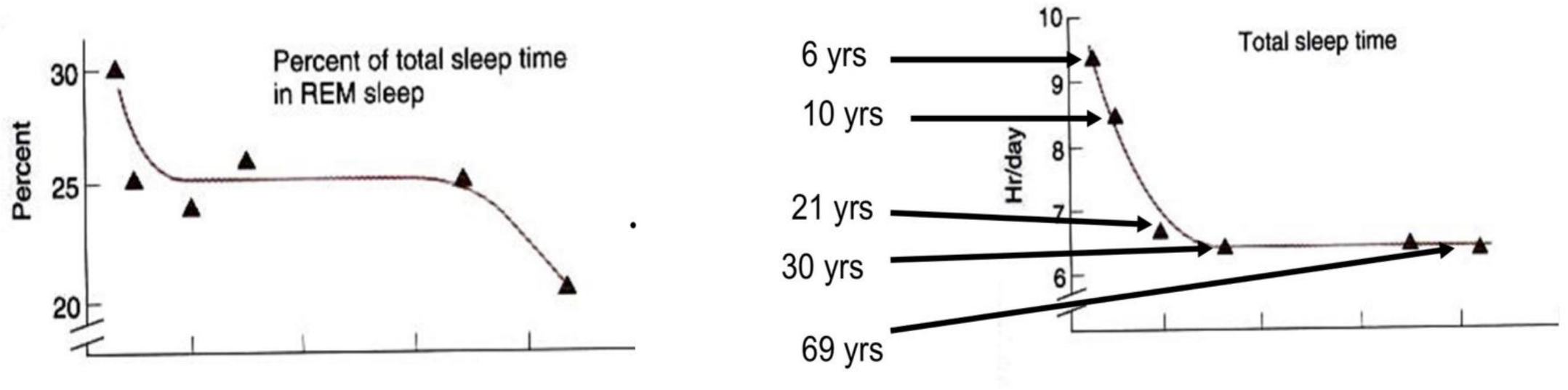


Figure 7-11 Showing Normal sleep cycle at different ages.

REM step occupies (explain percent of total sleep time in R.E.M. Sleep)

80% of total sleep

Premature Infants

Full-Term Neonates

50% of total sleep

More sleep time and stage 4 than adults.

Children

20-69 years

20% of total sleep

Current Theories About The Neural Basis Of Sleep: (Dr. Nervana said JUST READ IT)

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.
4. Injections of Melatonin induce sleep.
5. Stimulation of the Supra-chiasmal Nucleus (SCN) of hypothalamus by light falling on the retina → inhibits Melatonin release from Pineal gland & produces wakefulness.

Role of Serotonin & Melatonin in SWS

(JUST READ IT)

1) Role of Serotonin in SWS

Raphe nucleus[1] (secret serotonin[2])

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

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).

Raphe Nucleus A group of nuclei located in the reticular formation of the medulla, pons & midbrain. Situated along the midline, contain serotonergic neurons.

PHYSIOLOGICAL MECHANISMS OF SLEEP AND WAKING (JUST READ IT)

Acetylcholine

neurotransmitters involved in arousal.

Two groups of acetylcholinergic neurons are located in pons & basal forebrain, produce activation & cortical desynchrony when they are stimulated.

Muramyl peptide

Induces sleep

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

Figure 7-12[3,4]

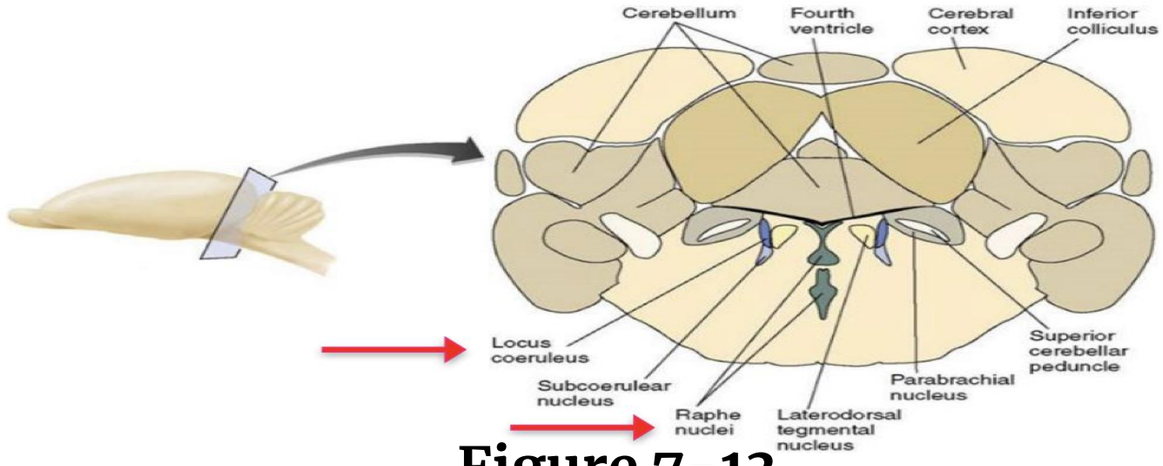


Figure 7-13

FOOTNOTES

1. Raphe nuclei are thin nuclei located below the level of mid pons and they are involved in many functions of CNS. They make local connections with the brainstem reticular formation and also they have upward connections with the thalamus, Hypothalamus and even the cerebral cortex specifically the neocortex. In addition, they have downward connections with the dorsal horn cells of the spinal cord grey matter.
2. Serotonin secretion in the local and upward connections is associated with producing sws by inhibitory signals and in the downward connections it will suppress sensory signals such as pain.
3. **Locus coeruleus:** 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.
4. Norepinephrine: catecholamine agonists produce arousal & sleeplessness effects appear to be mediated by the locus coeruleus in the dorsal pons.

SLEEP DISORDERS

Dr. Nervana mentioned insomnia, somnolence, Sleep apnea, and drug dependency insomnia only. She skipped the rest.

INSOMNIA

"habitual sleeplessness; inability to sleep".

- No single definition of insomnia.
- One of the most important causes of insomnia is sleep medications.
- Not a disease, but rather a symptom of pain, discomfort or other physical ailment.

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 (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 PARALYSIS

A symptom of narcolepsy; paralysis occurring just before a person falls asleep.

DRUG DEPENDENCE INSOMNIA

Caused by the side effects of ever increasing dependency doses of sleeping medications.

SLEEP ATTACK

A symptom of narcolepsy; an irresistible urge to sleep during the day, after which the person awakes feeling refreshed.

CATAPLEXY

"Sudden loss of voluntary muscle tone".
A symptom of narcolepsy; complete paralysis that occurs during waking.

HYPNAGOGIC HALLUCINATION

A symptom of narcolepsy; vivid dreams that occur just before a person falls asleep; accompanied by sleep paralysis.

REM SLEEP BEHAVIOUR

A neurological disorder in which a person doesn't become paralyzed during REM sleep and thus acts out dreams.

REM SLEEP DISORDERS

a. Nightmare = frightening dream
b. Sleep paralysis = awake but unable to speak or move
c. Sleep sickness

NIGHT TERROR

Sudden arousal from sleep and intense fear accompanied by physiological reactions (e.g., rapid heart rate, perspiration) that occur during slow-wave sleep.

DISORDER OF SLOW-WAVE SLEEP

Sleep talking / sleep walking [common in children]

NIGHT TREMORS

Are seen in III, IV stage of slow wave sleep [common in children].

SOMNAMBULISM

Walking during sleep.

NIGHTMARES

Frightening dreams, awake from REM.

QUIZ

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1. REM sleep accupies .... of the total sleep of full-term neonates:
A) 80%
B) 50%
C) 25%
D) 15%

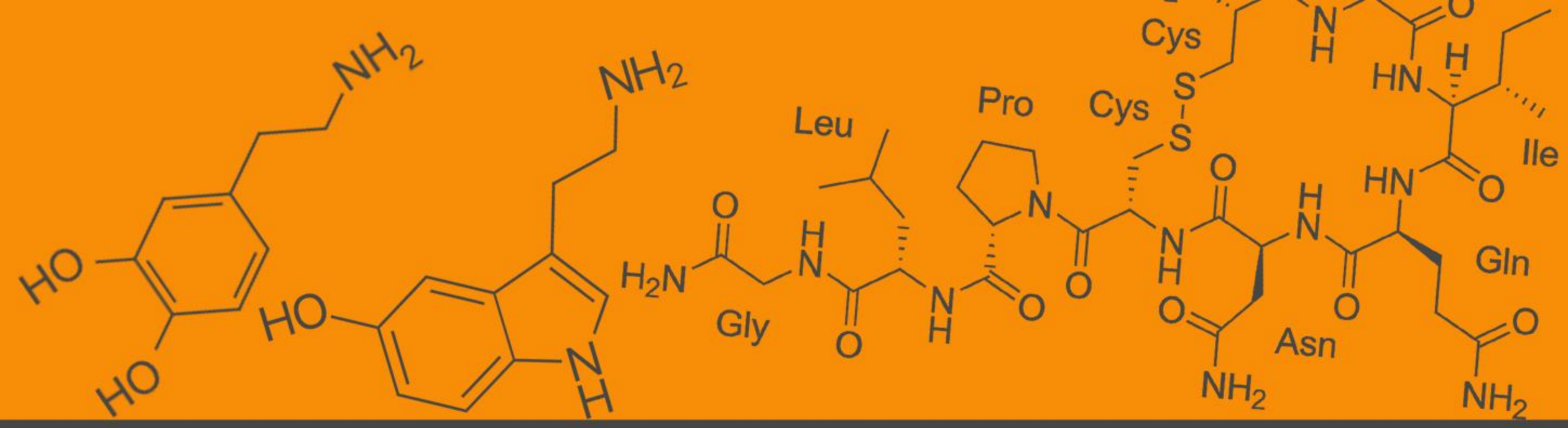
2. During sleeping which of body's secretions are reduced?
A) gastric.
B) Salivary.
C)lacrimal.
D) Both B & C.

3. 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.

4. An experimental drug is administered intravenously to 6 healthy volunteers. A unanimous finding in all 6 volunteers is decreased induction of sleep. A decrease in production of which substance is most likely in these volunteers after treatment with the experimental drug?
A) Acetylcholine
B) Dopamine
C) Glutamate
D) Norepinephrine
E) Serotonin

5. 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

ANSWER KEY: B, D, D, E, D



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