

## SLEEP

Before complaining, realize that this handout covers **TWO** lectures!

Sleep is a universal behavior that has been demonstrated in every animal species studied, from insects to mammals. It is one of the most significant of human behaviors, occupying roughly one-third of our lives. Although the exact functions of sleep are still unknown, it is clearly necessary for survival since prolonged sleep deprivation leads to severe physical and cognitive impairment, and finally death. Sleep is particularly relevant to medicine because sleep disturbances occur in virtually all psychiatric illnesses and are frequently part of the diagnostic criteria for specific disorders.

### Definition of sleep

From a behavioral standpoint, sleep is a state of decreased awareness of environmental stimuli that is distinguished from states such as coma or hibernation by its relatively rapid reversibility. Sleeping individuals move little and tend to adopt stereotypic postures. Although sleep is characterized by a relative unconsciousness of the external world and a general lack of memory of the state, unlike people who have been comatose, we generally recognize when we feel sleepy and are aware that we have been asleep at the termination of an episode.

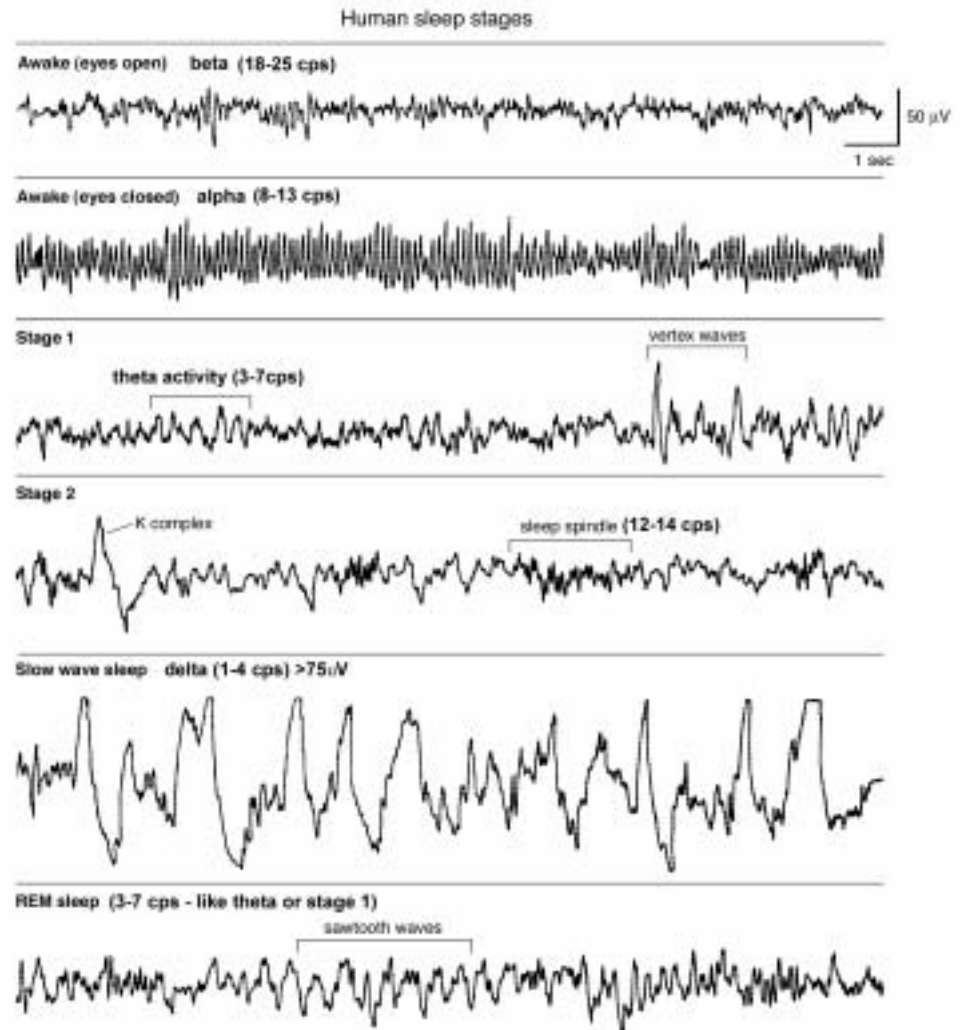
For clinical and research purposes, sleep is generally defined by combining behavioral observation with electrophysiological recording. Humans, like most other mammals, express two types of sleep: **rapid eye movement (REM) and non-rapid eye movement (NREM)** sleep. These states have distinctive neurophysiological and psychophysiological characteristics. REM sleep derives its name from the frequent bursts of eye movement activity that occur. It is also referred to as **paradoxical sleep** because the electroencephalogram (EEG) during REM sleep is similar to that of waking. In infants, the equivalent of REM sleep is called **active sleep** because of prominent phasic muscle twitches. NREM sleep, or **orthodox sleep**, is characterized by decreased activation of the EEG; in infants it is called **quiet sleep** because of the relative lack of motor activity.

### Stages of sleep

Within REM and NREM sleep, there are further classifications called **stages**. For clinical and research applications, sleep is typically scored in epochs of 30 seconds with stages of sleep defined by the visual scoring of three parameters: EEG, electrooculogram (EOG) and electromyogram (EMG) recorded beneath the chin. During wakefulness, the EEG shows a low voltage fast activity or activated pattern. Voluntary eye movements and eye blinks are obvious. The EMG has a high tonic activity with additional phasic activity

related to voluntary movements. When the eyes are closed in preparation for sleep, alpha activity (8-13 cycles per second [cps]) becomes prominent, particularly in occipital regions.

NREM sleep, which usually precedes REM sleep, is subdivided into four stages. Sleep is usually entered through a transitional state, stage 1 sleep, characterized by loss of alpha activity and the appearance of a low voltage mixed frequency EEG pattern with prominent **theta activity** (3-7 cps) and occasional vertex sharp waves may also appear. Eye movements become slow and rolling, and skeletal muscle tone relaxes. Subjectively, stage 1 may not be perceived as sleep although there is a decreased awareness of sensory stimuli, particularly visual, and mental activity becomes more dream-like.

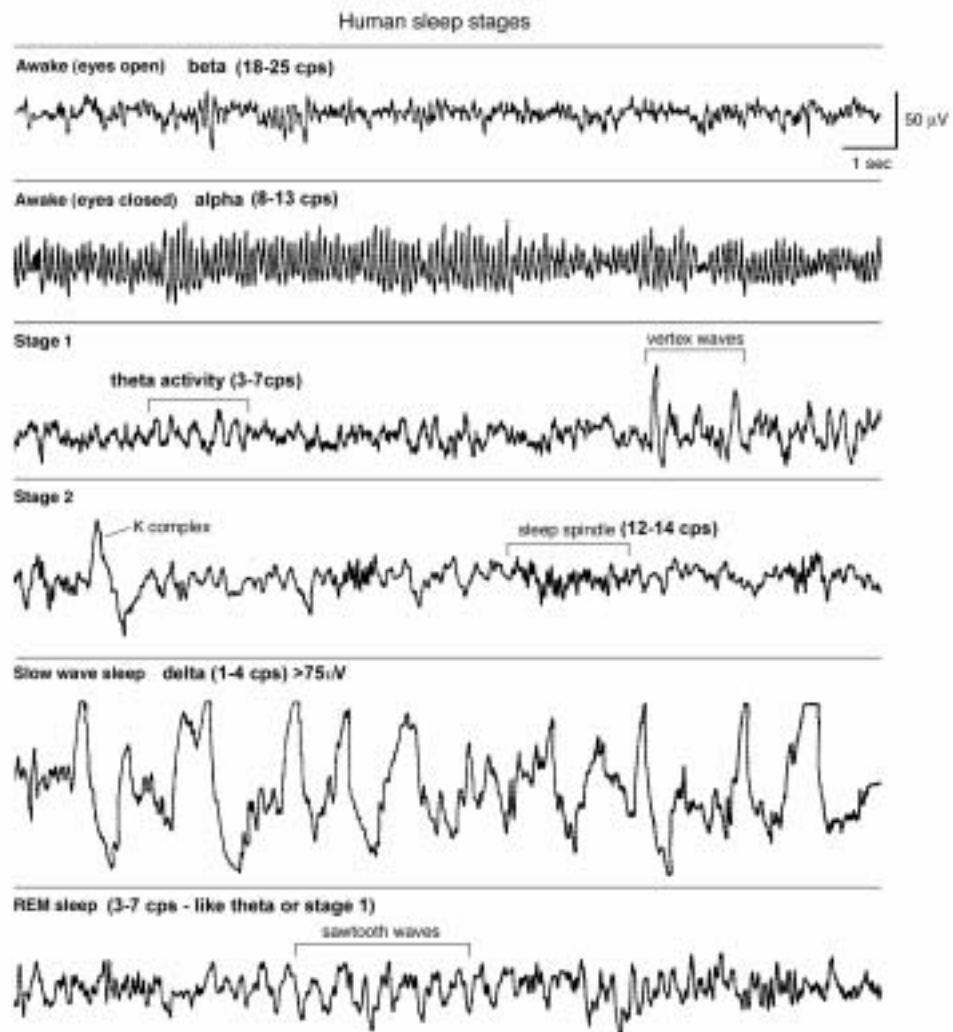


Motor activity may persist for a number of seconds during stage 1. Occasionally individuals experience sudden muscle contractions, sometimes accompanied by a sense of falling and/or dreamlike imagery; these hypnic (hypnosis = mental state like sleep) jerks are generally benign and may be exacerbated by sleep deprivation.

After a few minutes of stage 1, sleep usually progresses to stage 2, which is heralded by the appearance of **sleep spindles** (12-14 cps) and **K-complexes** (high amplitude negative sharp waves followed by positive slow waves) in the EEG. Stage 2 and subsequent stages of NREM and REM sleep are all subjectively perceived as sleep. Particularly at the beginning of the night, stage 2 is generally followed by a period comprised of stages 3 and 4. Slow waves ( $\leq 2$  cps in humans) appear during these stages, which are subdivided according to the proportion of delta waves in the epoch; stage 3 requires a minimum of 20% and not more than 50% of the epoch time occupied by slow waves, whereas stage 4 is scored with greater than 50% of the epoch showing slow wave

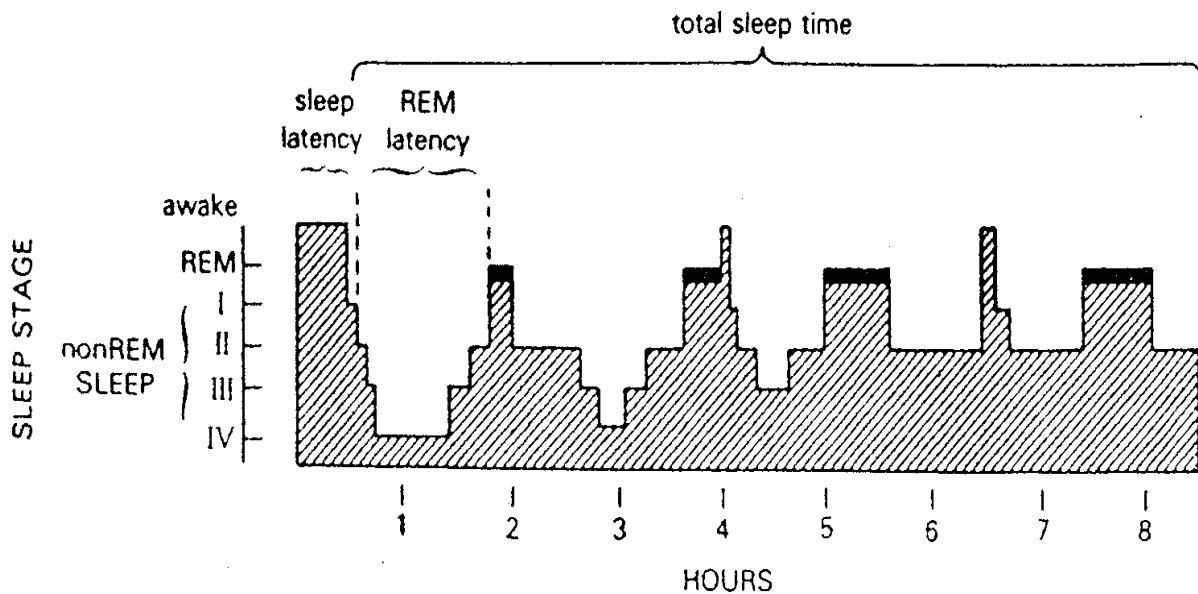
activity. Stage 3 and 4 are also referred to as **slow wave sleep** (SWS), **delta sleep**, or **deep sleep**, since arousal threshold increases incrementally from stages 1 through 4. Eye movements cease during stages 2-4, and EMG activity decreases further.

REM sleep is not subdivided into stages, but is rather described in terms of **tonic** (persistent) and **phasic** (episodic) components. Tonic aspects of REM sleep include the activated EEG similar to that of stage 1, which may exhibit increased activity in the theta band (3-7 cps), and a generalized atonia of skeletal muscles except for the extraocular muscles and the diaphragm. Phasic features of REM include irregular bursts of rapid eye movements and muscle twitches.



### Organization of sleep

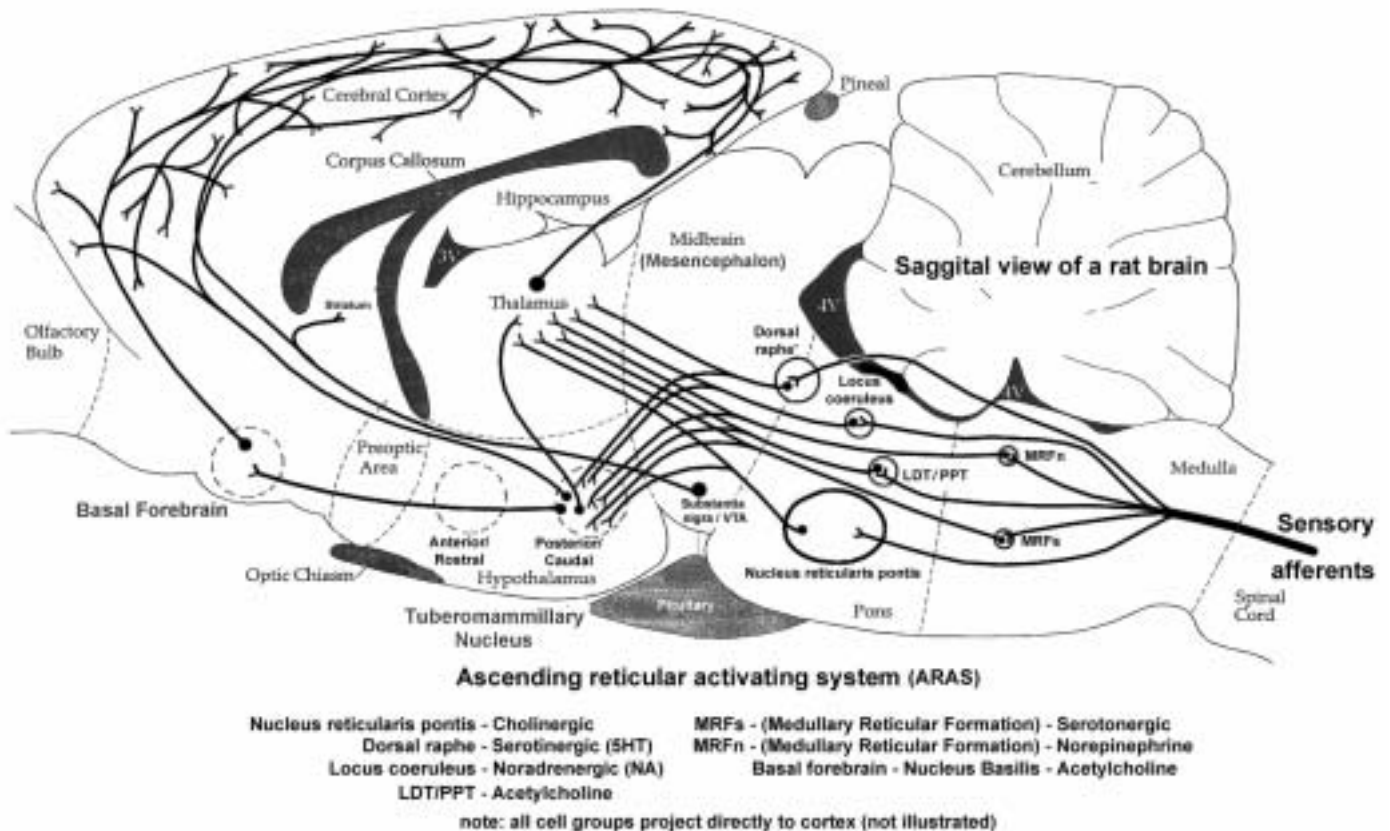
The amount of sleep obtained during the night varies among individuals; most adults need about 7-9 hours of sleep per night to function optimally, although there exist short sleepers who appear to function adequately with less than 6 hours per night, as well as long sleepers who may need 12 or more hours per night. In addition to genetic factors that influence daily sleep needs, age and medical or psychiatric disorders also strongly influence sleep patterns. Regardless of the number of hours needed, the proportion of time spent in each stage and the pattern of stages across the night is fairly consistent in normal adults. A healthy young Med 1 will typically spend about 5% of the sleep period in stage 1 sleep, about 50% in stage 2, and 20-25% in each of SWS (stages 3 and 4) and REM sleep. Sleep occurs in cycles of NREM-REM sleep, each lasting approximately 90-110 minutes. SWS (stages 3 and 4) is most prominent early in the night, especially during the first NREM period, and diminishes as the night progresses. As SWS wanes, periods of REM sleep lengthen, while showing greater phasic activity and generally more intense dreaming later in the night.



## Circuitry and Neurotransmitters Underlying Wakefulness, NREM and REM Sleep

### Wakefulness

As mention earlier, wakefulness is associated with a low-voltage/fast-frequency EEG (also known as "activated" or "desynchronized"). The **ascending reticular activating system** (ARAS) maintains an activated EEG/cortex. Ascending projections from the medulla, pons, and midbrain travel in the ARAS. These pathways arise from cholinergic cell groups in the pons called lateral dorsal tegmental (LDT), pedunculopontine tegmental (PPT) and nucleus reticularis pontis (NRP; oralis and caudalis). Other ascending axons arise from serotonergic cell groups at the midbrain-pons junction, the dorsal raphe (DR), and medulla (MRFs; see abbreviation in diagram below). Another contribution to the ascending system arises from cells containing norepinephrine; the cells are in the locus coeruleus (LC) and medulla (MRFn). A final "member" of the ascending activating system is comprised of axons of dopaminergic (DA) cells in the substantia nigra pars compacta and ventral tegmental area (VTA).



Axons in the ARAS pass directly to the cortex (not illustrated), where they activate the EEG/cortex. The ascending system also innervates the intralaminar nuclei of the thalamus, which in turn project to cortex and activate the EEG/cortex. DA projections reach the striatum (caudate and putamen) and frontal cortex (mesocorticolimbic projections of VTA) and activate the EEG/cortex. Another group of ascending axons reaches the posterior/caudal hypothalamus. One important cell group in this area is the tuberomammillary nucleus (TM), which is histaminergic and projects to the thalamus and

cortex. Other cells in the posterior hypothalamus project to the basal forebrain (nucleus of Meynert). Cholinergic cells in the nucleus project to and activate the cortex/EEG.

It should not be surprising that transection of the brain stem at the level of the midbrain interrupts all of the fibers in the ARAS and results in a state indistinguishable from non-REM sleep.

It has long been known that drugs such as amphetamine and cocaine, which enhance the release or synaptic concentrations of DA and NE, dramatically enhance and prolong wakefulness. Acetylcholine is released from nerve terminals in the thalamus and cortex in highest concentrations in association with cortical activation that occurs naturally during wakefulness. Nicotine (a cholinergic agonist), and anticholinesterase inhibitors (e.g., neostigmine) have long been known to enhance arousal. Blockers of both nicotinic, and even more so of muscarinic cholinergic receptors, diminish cortical activation and vigilance. Loss of cholinergic cells in Alzheimer's patients (in nucleus basalis of Meynert) is associated with slowing of the cortical EEG. Drugs with anticholinergic activity, including tricyclic antidepressants and atropine, can cause sedation and increase slow wave activity.

Histamine in the tuberomammillary nucleus (TM) also appears important for wakefulness. These neurons project in a diffuse manner to the thalamus and cerebral cortex (not illustrated). Drugs containing antihistamine produce drowsiness and a decrease in cortical activation. The significance of the posterior hypothalamus for waking was first revealed by Constantin von Economo in the early part of the 20<sup>th</sup> century when an outbreak of viral encephalitis (called encephalitis lethargica) resulted in damage to this region of the hypothalamus and in turn profound somnolence (sleep).

Serotonergic neurons, like LC neurons, fire at higher levels in waking, lower levels in NREM sleep, and fall silent during REM sleep. Selective serotonin reuptake inhibitors (SSRIs) tend to decrease sleep time and increase arousal during sleep.

A number of other neurotransmitters and neuromodulators appear to have wakefulness-promoting effects. These include substance P, neurotensin, epinephrine, and hypothalamic peptides such as corticotropin releasing factor, vasoactive intestinal peptide and thyrotropin releasing factor, all of which can increase arousal levels. Cortisol also promotes wakefulness. It is thus possible that sleep disturbance in depression including early morning awakening could be related in part to the associated hyperactivity of the HPA axis.

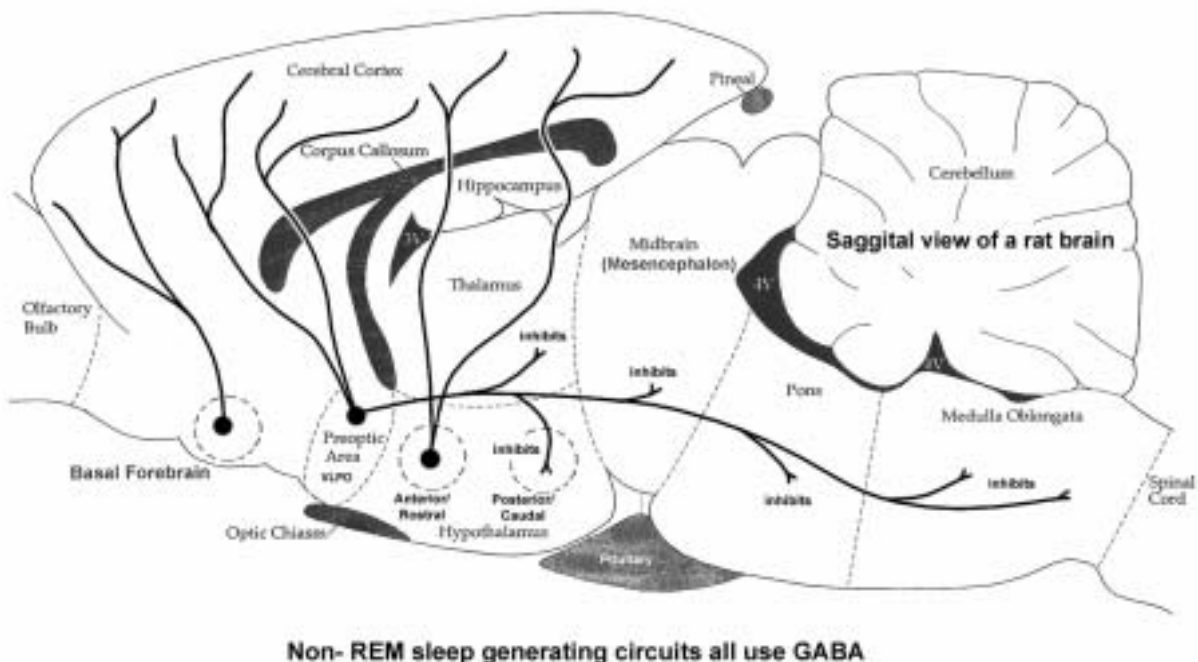
### **Non-Rem Sleep**

The initiation of non-REM sleep probably begins with the emergence of inhibitory signals from the ventrolateral preoptic area (VLPO). The preoptic area lies just rostral to the optic chiasm (it is a part of the hypothalamus). VLPO neurons are sleep-active in that they increase their discharge selectively at sleep onset. The VLPO cells contain GABA and project to serotonergic, noradrenergic and cholinergic cell groups in the brain stem reticular formation and histaminergic populations in the TM, i.e., posterior/caudal hypothalamus. These wake-promoting neurons in the brain stem show progressive

reductions in activity across sleep stages as VLPO neurons show progressive activation. Therefore, activation of VLPO neurons induces inhibition of the wake-promoting neuronal cells associated with the ARAS. Interestingly, the brain stem wake-promoting cells feed back and inhibit the VLPO sleep-promoting neurons. Thus, a sleep process starting with activation of the VLPO region would inhibit wake-promoting systems, which would remove inhibition from VLPO neurons, facilitating the sleep-onset process. On the other hand, an arousing input mediated by wake-promoting neurons would inhibit VLPO neurons, which would then remove inhibition from wake-promoting neurons. In this way, the system can switch decisively between sleep and waking, and also tend to maintain sustained sleep and wake states. Adenosine has long been known to be sleep promoting and its effects are blocked by caffeine. It is reasonable to expect that adenosine is a “sleep factor” that may directly or indirectly regulate the activity of VLPO neurons. Further studies are needed to complete the story but investigators have hypothesized that adenosine, a neuromodulator, increases during metabolic activity.

Recently the importance of the peptide hypocretin (orexin) in the maintenance of wakefulness was defined through discovering its role in the disorder narcolepsy. Hypocretin is produced by cells in the hypothalamus that provide excitatory input to all components of the ARAS, (not shown on drawings). Animal models of narcolepsy are related to deficits in the hypocretin system; canine narcolepsy is caused by a mutation in the hypocretin type 2 receptor gene.

In addition to inhibition of the ARAS by the VLPO, other regions of the hypothalamus and forebrain participate in NREM sleep. In particular the anterior/rostral hypothalamus, pre-optic area, and nucleus basalis all contain GABA-ergic neurons that project to cortex and participate in the control of non-REM sleep. GABA has long been thought to play a role in sleep, particularly in view of the sedative effects of the

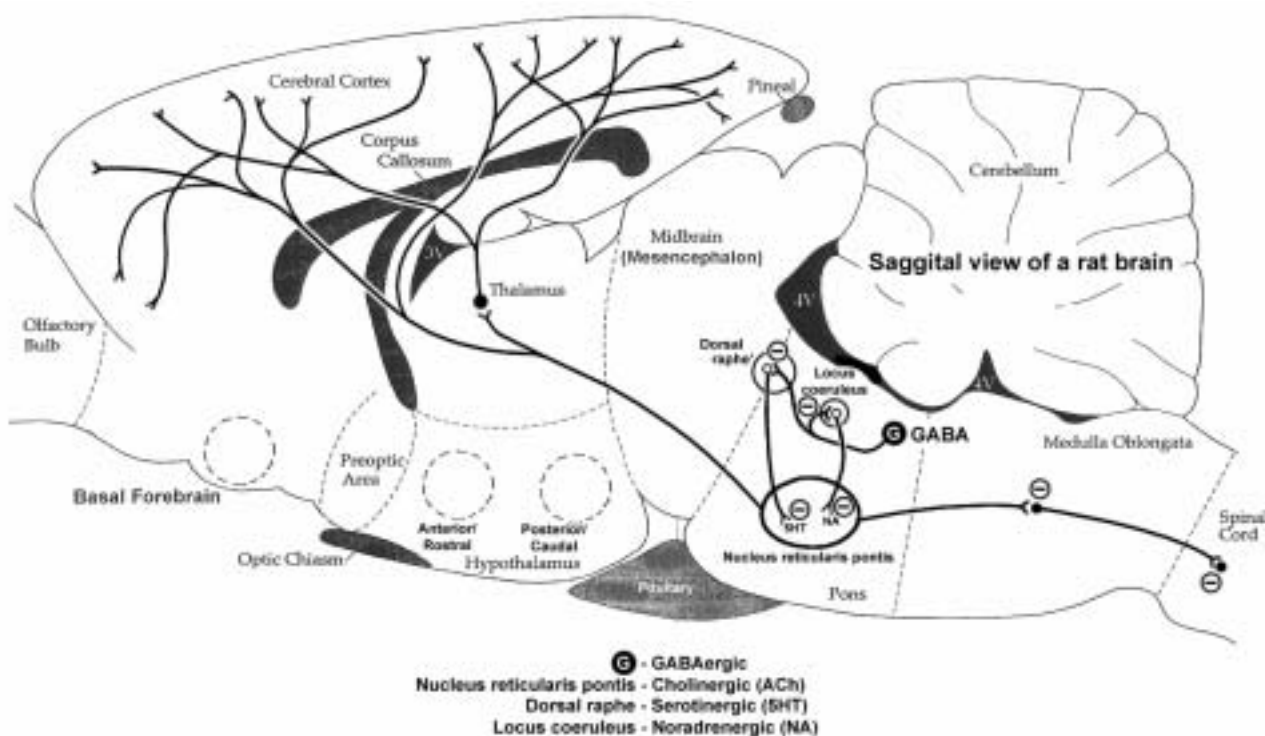


benzodiazepines (Valium), which are known to enhance the postsynaptic action of GABA. Similarly, barbiturates produce sedation and in high doses, anesthesia. It should not be surprising that GABA is released from the cerebral cortex in the highest concentration during NREM sleep.

## REM Sleep

The EEG of REM sleep closely resembles the EEG of active wakefulness, and in some species they are virtually indistinguishable. This is a surprising finding, considering that these two states could not be more different behaviorally. As mentioned earlier, phasic (episodic) and tonic (persistent) REM sleep are often distinguished. Phasic REM sleep events are intermittent (e.g., rapid eye movements and muscle twitches). Tonic REM sleep events are persistent (e.g., desynchronized [activated EEG] and striated [voluntary] muscle inhibition.) There is a flaccid paralysis of major muscle groups.

Areas involved in REM sleep generation lie primarily in the pons. The cholinergic neurons in nucleus reticularis pontis participate in the generation of REM sleep via their projections to thalamus and cortex. Cells in the LC and DR inhibit the cholinergic cells in reticularis pontis during waking and NREM sleep. The transition between NREM and REM sleep is thought to depend upon GABA-ergic inhibition of LC and DR (which will no longer inhibit reticularis pontis); little is known about the inputs to these GABA cells. When these GABA cells stop firing, NREM returns and wakefulness can occur when sensory stimulation occurs and the ARAS kicks in. The cholinergic neurons in reticularis pontis have descending projections to the brain stem and spinal cord that inhibit movement during the tonic phase of REM.





There is some evidence to indicate that the motor paralysis of tonic REM sleep may be protective against the acting out of one's dreams; if the brain stem mechanisms subserving this state-dependent paralysis are damaged, truly bizarre sleep behaviors can occur. Individuals have been described who suffer from a clinically defined syndrome called REM Behavior Disorder. These patients exhibit normal behavior during wakefulness and NREM sleep. But during REM sleep they are not paralyzed, as are normal individuals. Rather, they appear to act out their dreams. One man dreamed that he was a linebacker for a successful football team and leapt out of bed and crashed into a wall. His behavior would have been appropriate had the wall been an opposing player. In yet another abnormality of motor functioning during REM sleep, the mechanisms that produce REM sleep paralysis can erupt during wakefulness, as in cataplexy. These patients, although they are awake, experience a sudden withdrawal of motor activity and can literally collapse to the floor.

### Physiological Changes Associated with Sleep

During NREM sleep and tonic REM sleep, there is a relative **increase** in parasympathetic activity relative to sympathetic activity. The autonomic nervous system reaches its most stable state during SWS in comparison to wakefulness. During **phasic REM sleep**, however, there are brief surges in both sympathetic and parasympathetic activity, resulting in a high degree of **autonomic instability**.

Blood pressure, heart rate, and cardiac output decrease during NREM sleep, reaching their lowest average values and least variability in SWS. Although these parameters remain reduced on average during REM sleep in comparison to waking, they attain their **peak** values during **REM**. Arrhythmias are also more prevalent in REM sleep.

Temporary breathing instability and/or periodic breathing may occur at the onset of sleep. Respiratory rate and minute ventilation decrease during sleep, and upper airway resistance increases as a result of muscle relaxation, most significantly during REM sleep. These changes contribute to exacerbations of underlying pulmonary disease as well as sleep-related breathing disorders such as sleep apnea.

Brain and body temperature are down-regulated during NREM sleep, particularly SWS, as a result of a decreased hypothalamic temperature set point as well as active heat loss. People commonly experience this phenomenon when they go to sleep feeling somewhat cold and wake up several hours later to throw off their extra covers because they feel too warm. During REM sleep, there is a decreased ability to regulate body temperature through sweating and shivering.

Most hormones show significant interactions with sleep-wakefulness patterns. **Growth hormone** (GH) is released primarily during the early part of the night and its secretion is enhanced by SWS. Sleep also stimulates **prolactin** secretion, although prolactin peaks after GH, usually during the middle portion of the night. Pulses of growth hormone and prolactin can occur after the onset of sleep, regardless of its timing,

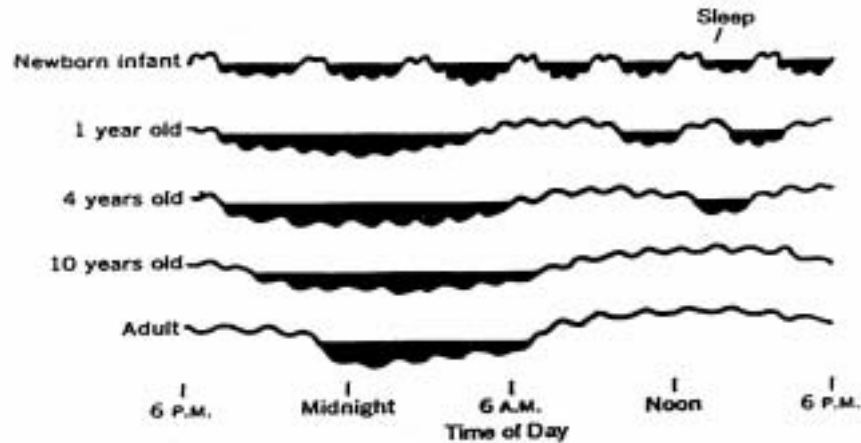
however. Both GH and prolactin may have feedback effects on sleep as well; GH seems to enhance SWS, whereas prolactin may increase REM sleep. In contrast, **thyroid stimulating hormone** (TSH) reaches its peak level in the evening just prior to sleep onset; its secretion is inhibited by sleep and stimulated by sleep deprivation. The **hypothalamic-pituitary-adrenal axis** (HPA axis) is usually at its most inactive state at nocturnal sleep onset. Sleep onset inhibits cortisol release, whereas **adrenocorticotrophic hormone** (*ACTH*) and **cortisol** levels rise at the end of the sleep period, shortly before awakening and likely contribute to morning arousal. Severe sleep disruption or sleep deprivation may have significant clinical effects on the endocrine system; for example, patients with obstructive sleep apnea show decreased levels of GH and prolactin, and sleep deprivation produces evidence of HPA axis activation in the evening of the day following deprivation.

One of the characteristics of REM sleep in men is the occurrence of penile erections, beginning in infancy and persisting into old age. Nocturnal penile tumescence studies are therefore helpful in determining whether cases of impotence are related to organic or psychogenic etiologies. In women, REM sleep produces increased vaginal blood flow and clitoral erection. These changes are not necessarily linked to sexual content in associated dreams.

### **Developmental Course of Sleep**

Generally speaking, age is probably the single most crucial factor (apart from the time since the last episode of sleep) that determines how humans characteristically sleep. More so than gender, psychiatric illness and even, to a large extent, most physical illnesses, age is a major determinant of human sleep. Across the human life span, sleep undergoes a wide variety of modifications that are broadly typical of the species, although for any particular aspect of sleep, at any given age, sleep measures have a relatively normal (bell-shaped) distribution. For example, the amount of nocturnal sleep (7-8 hours) obtained by the majority of Med 1s occupies the mid-point of such a distribution with some individuals obtaining less sleep and some individuals obtaining more sleep. In the age-related patterns of sleep that are discussed below, the data are normative, i.e., they represent group values.

The newborn infant sleeps about 16-18 hours per day, and its sleep is widely distributed around the twenty-four hour day. This high sleep requirement is assumed to reflect a non-specific restitutorial (repayment) demand that occurs as a result of dramatic growth. This daily sleep quota remains relatively constant for the first year of life. A further gradual decline to about ten to twelve hours occurs between three and five years of age. By age ten, sleep amounts of ten hours or less are reported; sleep then continues to decrease throughout adolescence until the adult pattern is approximated. Paralleling these decreased sleep amounts throughout adolescence are increases in the daytime tendency to fall asleep. Thus, the adolescent decrease in sleep duration may not represent a decrease in sleep need because the decreased sleep duration is accompanied by increased daytime sleepiness.



Polyphasic (multiphase) sleep following birth changes first to biphasic (two-phase) sleep among preschool children and later to monophasic (single-phase) sleep. Among the elderly, periods of sleep during the day become more frequent again.

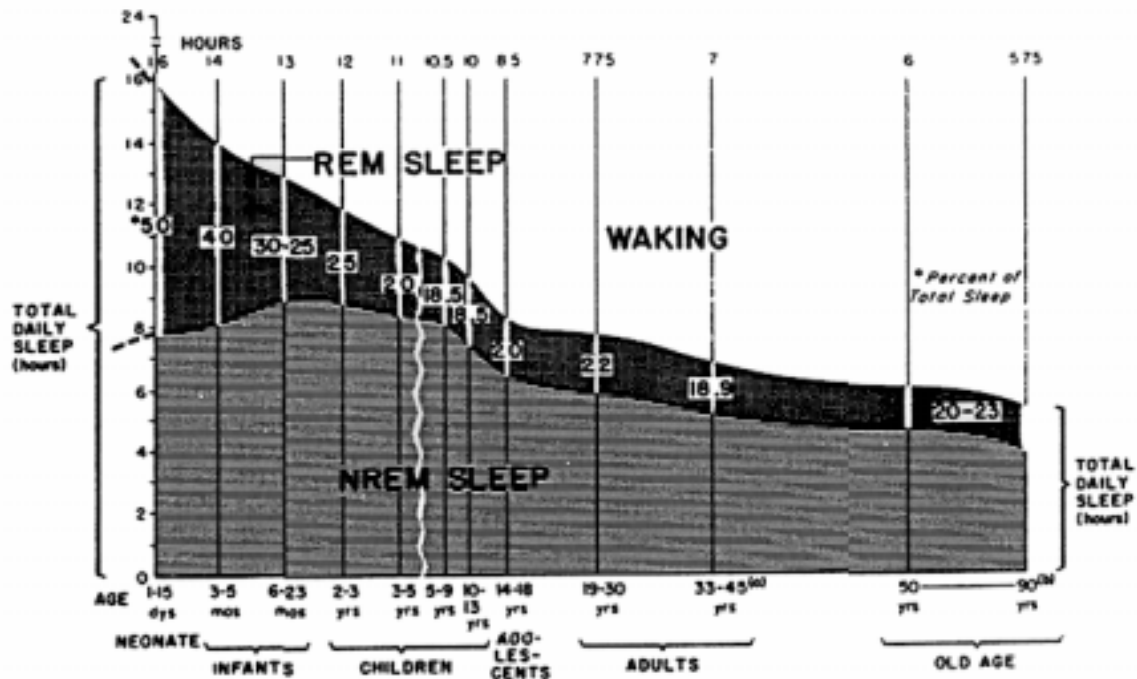
Most evidence indicates that as individuals approach old age, the amount of nocturnal sleep decreases; older individuals usually sleep only six to seven hours. Also their sleep is more fragmented by wakefulness and is more susceptible to disruption by noise. One interpretation of these findings is that sleep need is decreased in older individuals. However, inferences about sleep need from sleep duration can be misleading. While decreased sleep is consistent with a decreased need to sleep, decreased sleep is also consistent with the decreased capacity of the “sleep mechanism” to meet normal sleep requirements. The decreased nocturnal sleep of older individuals may be partially offset by increased daytime napping. As a result, the 24 hour total sleep time of young and old adults may be quite similar.

### Developmental Course of REM Sleep

The quantity of REM sleep (defined as the proportion of total sleep time) may exceed 50% in the newborn; premature babies have even higher amounts. REM sleep amount declines throughout the first year of life. By the time a child is about two years of age, REM occupies about twenty to twenty five percent of total sleep, a figure that remains relatively constant throughout childhood, adolescence and adulthood. The reasons for the high levels of REM in the neonate are unclear, though it has been speculated that REM sleep is important for the maturation of the cerebral cortex and the oculomotor (eye movement) system, and that it assists in the programming of developing neuronal circuits.

Ontogenetic changes in REM sleep are not limited to the amount of REM sleep. The alternation of NREM and REM sleep, which occurs at approximately 90-100 minute intervals in middle-aged adults, occurs at 50-60 minute intervals in human infants. Infants

also may pass directly from wakefulness to REM sleep, thereby bypassing the first NREM cycle at the beginning of the night. There are some suggestions that in certain conditions of



pathological aging (e.g., Alzheimer's Disease) REM sleep may be reduced and that this reduction may reflect the decline in cholinergic function that occurs in this disorder.

Stages 3 and 4 of NREM sleep (i.e., synchronized, delta wave sleep, slow wave sleep) show a steady decrease across the lifespan. By three to five years of age, children typically have abundant, high amplitude (synchronized) delta wave sleep, which is relatively impervious to noise and external disruptions. This is the "restful" component of sleep that makes you feel refreshed after sleeping. Beginning in early adolescence, there is a gradual decline in delta wave sleep. Even within college age populations, this age-related decline can be observed. This decline continues throughout adulthood. This decrease in Stages 3 and 4 sleep is generally replaced by NREM Stages 1 and 2. By the time the average human reaches age 75, Stage 4 sleep, the sleep with the most abundant delta waves, may be virtually absent. The functional significance of the age-related decline in human delta activity during sleep is unknown, but the decline may represent one of the earliest known indicators of the aging of the central nervous system. Narcolepsy (intermittent episodes of uncontrollable sleep), thought to afflict one individual in 10,000, also typically begins in adolescence. In adulthood, insomnia is by far the most prevalent sleep disorder; its estimated prevalence increases from about 25% at age 30 to over 50% at age 70. Aged individuals are particularly susceptible to awakening during the night and then being unable to return to sleep. Both periodic leg movements (sometimes called nocturnal myoclonus) and sleep apnea (cessation of breathing for 15-30 seconds) occurs in 20-30% of people who are more than 65 years old.

## Temporal Regulation of Sleep and Wakefulness

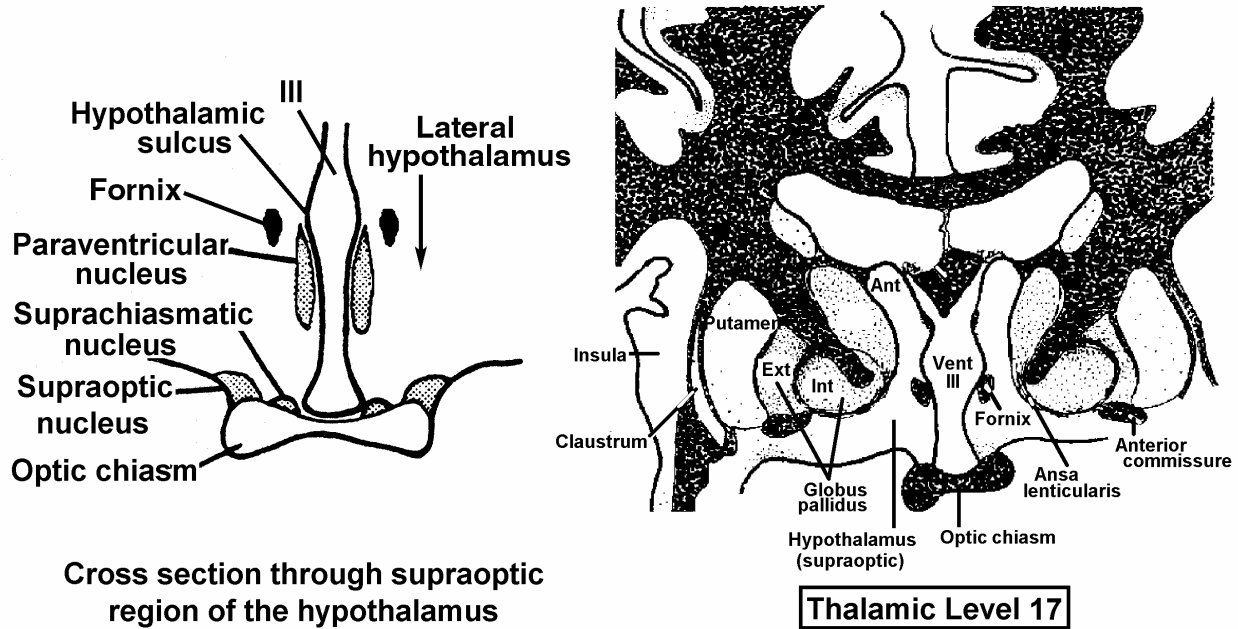
Cycles of peaks of activity (and troughs of inactivity) occur at various intervals. The cycle time between successive peaks (or troughs) is called the **period** of the cycle and the extent of the increase (or decrease) is called the amplitude. A period can be as short as a micro-second or as long as a year (circannual rhythm). In humans, rhythms with a period of “**about 24 hours**” (**circadian**) are of particular interest.

It is clear that peaks of activity of various physiological systems vary systematically with the time of day. Thus, the core body temperature of humans is not fixed at 98.6° Fahrenheit, but rather it is actively maintained near **100° at mid-afternoon** and near **96° in the early morning** hours before awakening. A similar pattern can be seen in plasma levels of hormones such as cortisol, growth hormone and prolactin, as well as in urine production, heart rate, and blood pressure.

Two important features are common to all diurnal (happening over a period of a day) rhythms. First, it is clear that a rhythmic organization of activity persists even in the **absence** of *environmental time cues* (blowing horns, lights, noise of lawnmowers etc.), which are collectively termed “**zeitgebers.**” Second, in the absence of these environmental time cues, the period length of the activity rhythm (the time from the onset of one bout of activity to the next) is **never** exactly 24 hours. This non-24 hour period length, which is a consistent feature of diurnal rhythms when observed in the **absence** of zeitgebers, is the origin of the term **circadian** (from circa meaning “**approximately**” and **dies** meaning “day”). Entrainment (“getting on board”) to the 24-hour environmental cycle results from daily resetting in response to the **zeitgeber** signals

The persistence of a daily, i.e., circadian, rhythmicity in the absence of environmental time cues provides convincing evidence that **circadian rhythmicity arises from within the organism** and that it is **not** a passive reflection of external environment influences (zeitgebers). One important corollary of this conclusion is that somewhere in the organism there must be a circadian “clock” that is responsible for the generation of circadian rhythmicity.

The principle mammalian circadian clock is located in the rostral hypothalamus, and specifically in the **suprachiasmatic nucleus**. Direct projections from the retinae reach the suprachiasmatic nucleus and it has been shown that lesions of the SCN render animals **arrhythmic** without any evidence of circadian organization. Transplantation of fetal SCN into the brains of adult animals that had previously been rendered arrhythmic by SCN destruction resulted in the restoration of circadian rhythmicity. Thus, the **circadian clock** was discovered to reside in the **suprachiasmatic nucleus** of the **hypothalamus**.



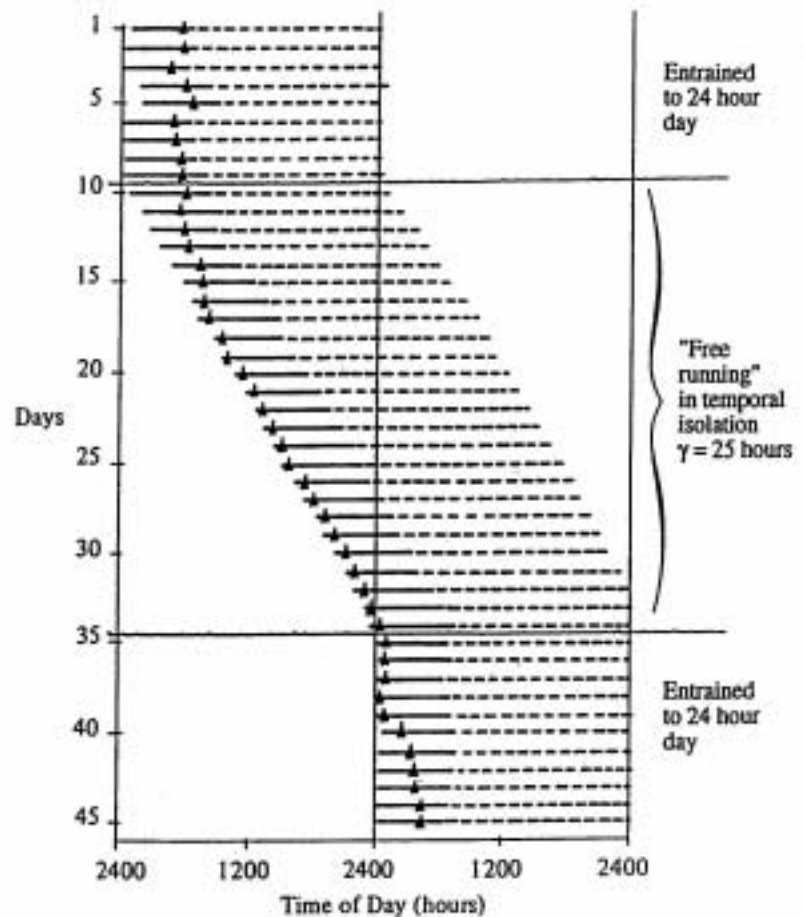
**Cross section through supraoptic region of the hypothalamus**

**Thalamic Level 17**

The **amount** of sleep and wakefulness **does not significantly change** when the SCN is destroyed, but the **normal 24-hour rhythm** of sleep and wakefulness is no longer present. Subjects have lived for up to six months in special apartments without windows, telephones, television, radio or any contact with the outside world that might provide a clue as to the time of day. In this **temporal isolation**, subjects are placed in an environment without time cues for periods of weeks to months. Although circadian rhythms of sleep persist, the “day length” as defined by the period between successive bedtimes is close to 25 hours. These results led to the conclusion that the endogenous period of the human circadian clock is about 25 hours and that the light-dark cycle serves to entrain it to the 24-hour day.

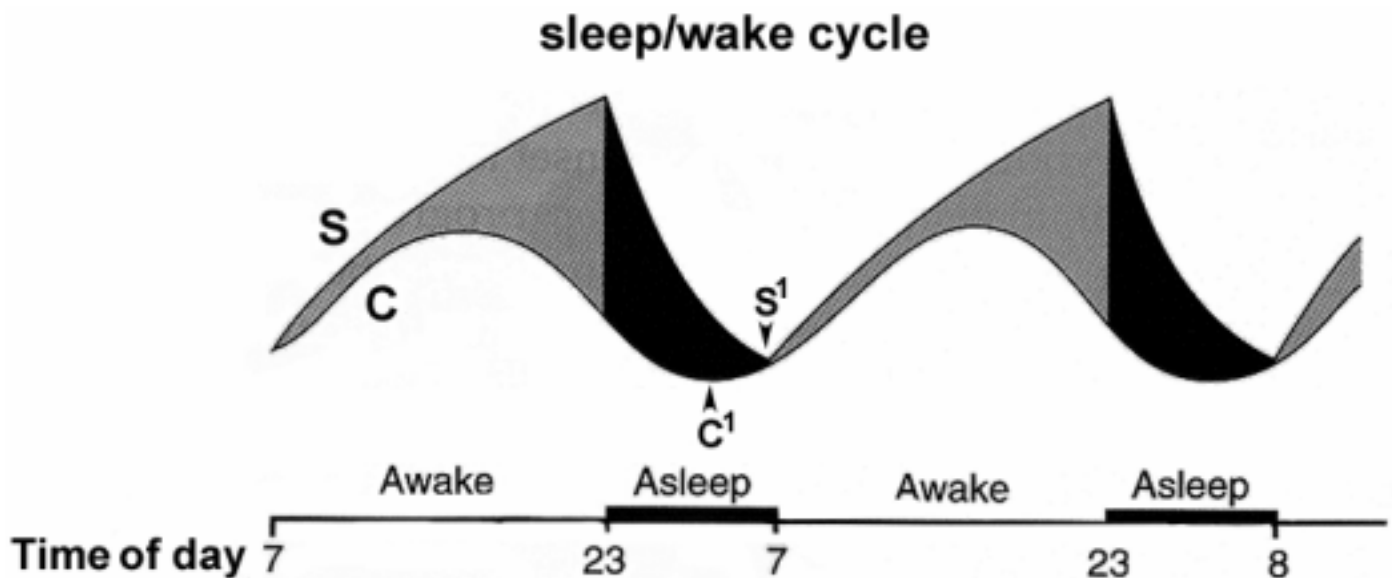
Under these temporal isolation conditions diurnal rhythms of sleep, activity, body temperature, hormone secretion and a range of other variables persist, but they no longer exhibit a period length of 24 hours. In the case of the typical human subject, the “free-running period” of the circadian system is greater than 24 hours, usually **nearer to 25 hours**. Under these conditions the **circadian oscillation** in bodily functions **would continue**. It is **innate, internal**, built into the organism, and does **not** need to be “driven” from outside. However the **oscillation** would **no longer** be exactly **24 hours**. In an isolated environment, the individual would “**free run**.” The latter term applies when the circadian rhythm is no longer entrained to 24 hours by zeitgebers, but rather is oscillating at its own natural innate periodicity. The individual does things when he “feels like it.” What is remarkable is that in such a case, the sleep-wakefulness rhythm of the body shows a periodicity that is **close** to 24 hours. In the case we have illustrated, (temporal isolation) the internal clock of the individual has a natural rhythm of exactly **25 hours**. Thus, as he goes to bed when he becomes sleepy, his sleep starts about one hour later each night. During **24 days** in isolation he drifts 24 hours later so that he is going to sleep at midnight **again**.

Although it would not be exactly 25 hours, the natural oscillation of most people would probably be from about twenty-four and a half hours to twenty-five and a half hours. This is why the term circadian is so appropriate to describe these natural oscillations. When the subject is “free running,” the **body temperature rhythm changed** its phase relationship to sleep-wakefulness. Instead of reaching its low point toward the **end of sleep**, the low point occurred at the beginning of the sleep period. This change in the phase relationship between sleep and body temperature is due to the fact that **the greatest circadian propensity for sleep coincides with the temperature minimum, which is also the time of greatest REM sleep propensity** (remember, we have longer REM cycles early in the morning when our body temperature is lowest).



It should be noted that while the **temporal isolation** data have indicated a natural periodicity of approximately 25 hours, data using a more sophisticated protocol called **forced desynchrony** suggest that the periodicity is closer to 24 hours. We want you to be aware of these recent data but they do not change the overall concepts established by the temporal isolation experiments.

The regulation of sleep, both NREM and REM, involves at least two key components, a circadian one and a homeostatic one. The circadian component “process C” in the figure below is responsible for the change in sleep propensity that is tied to the time of day. It behaves like a clock in that it continues without having to be reset. The homeostatic component “process S” refers to the fact that the longer one stays awake, the greater the propensity to sleep, and it represents the essential aspect of sleep whose function remains mysterious. It (process S) behaves like an adjustable hourglass, filling more with increased wakefulness. Sleep pressure is based on the interaction between these two processes. Process S builds up across the day and decreases during sleep. The circadian process C for sleep propensity (greatest at trough;  $C^1$ ), on the other hand, reaches its peak during the latter half of the night. The onset of sleep occurs at the greatest separation between S and C and when the environmental milieu is conducive to sleep. As process S decays, through sleep, to the current level of process C, sleep terminates ( $S^1$ ).



It can be seen that sleep **onset** is primarily driven by process S, whereas process C maintains sleep through the latter part of the night. It is common for humans to have a brief period of arousal in the middle of the night, possibly related to a reduction in overall sleep drive from the fall in process S before process C has reached its maximal values ( $C^1$ ).

### Sleep Pathology

We know sleep is very important but we do not know why we need to sleep. Lack of sleep impairs our ability to function and lack of REM sleep can lead to a state in which hallucinations and irritability occur. So it is important that we sleep properly. There are a number of disease processes that are associated with abnormal sleep patterns and we will review two of them: **Narcolepsy** and **periodic limb movements of sleep**.



**Narcolepsy:** Narcolepsy is a relatively uncommon condition (0.03-0.1% of the population) but can have devastating effects on a person's life. The condition is characterized by **sudden attacks of sleep**. These often occur when attention levels are low but also can occur when driving and can lead to accidents. The attacks of sleep are characterized by sudden onset of REM sleep that last for 5-30 min. These patients may have a number of associated symptoms besides sleep attacks. One symptom is a sudden loss of muscle tone during which the patient may fall. This condition is called **cataplexy** and is often precipitated by a sudden emotional stimulus. Another symptom is **sleep paralysis** in which a patient who is either first falling asleep or just wakening cannot move. During these episodes of sleep paralysis, the patient may also experience **hypnagogic hallucinations**, visual or auditory hallucinations that may be frightening. These symptoms represent changes in neural integration that occur in REM sleep: atonia and dream-like sensations.

**Narcolepsy is diagnosed by the demonstration of REM-onset sleep in a person who is not REM sleep deprived.** Most patients also have a HLA DR2 subtype (remember that a number of genes define our histocompatibility and are termed human leukocyte antigens, HLA). As mentioned earlier, narcolepsy in dogs (especially Doberman pinschers) is associated with defect in the hypocretin system.

#### **Periodic limb movements of sleep and restless leg syndrome:**

Restless leg syndrome refers to the unpleasant crawling sensation that occurs in the legs and is most problematic at bedtime. This complaint increases with age and often is associated with a variety of other problems (including uremia, arthritis, and peripheral neuropathy). The person with restless leg syndrome has an irresistible urge to move their legs while at rest. They need to stretch or walk about to relieve the sensations. This interferes with falling asleep and usually is associated with another condition, periodic leg (limb) movements of sleep.

Periodic limb movements of sleep usually involve the lower extremities but may also occur in the upper extremity. Typically these movements involve combinations of extension of the big toe, dorsiflexion of the ankle, and flexion of the knee and hip. The movement appears to be a Babinski-like response. The movements appear to be mediated by brain stem or other lower centers that are active during wake-sleep transitions. The movements can arouse the patient or their bed partner. These movements are a common cause of insomnia. Treatment consists of GABAergic drugs (benzodiazepines or gabapentin), L-DOPA, dopamine agonists, or opiates.

**PROBLEM SOLVING**

1. Neurotransmitters involved in promoting wakefulness include all of the following

**EXCEPT:**

- A. adenosine
- B. dopamine
- C. acetylcholine
- D. histamine
- E. norepinephrine

2. Which of the following nuclei are GABA-ergic?

- A. LC
- B. dorsal raphe
- C. LTD
- D. PPT
- E. none of the above

3. Which of the following nuclei are cholinergic?

- A. LC
- B. dorsal raphe
- C. LTD
- D. PPT
- E. two of the above

4. Which of the following nuclei are serotonergic?

- A. LC
- B. dorsal raphe
- C. LTD
- D. PPT
- E. tuberomammillary

5. Which of the following nuclei/areas contain norepinephrine?

- A. preoptic area
- B. anterior/rostral hypothalamus
- C. nucleus basalis of Meynert
- D. reticularis pontis
- E. none of the above

6. Which of the following occur(s) following destruction of the ARAS in the midbrain?
- A. insomnia
  - B. constant REM sleep
  - C. an EEG consisting of beta waves
  - D. a flat EEG
  - E. NREM sleep
7. Which of the following statements is/are **TRUE**?
- A. nicotine enhances arousal
  - B. histamine enhances arousal
  - C. REM is called paradoxical sleep
  - D. caffeine blocks the effects of adenosine
  - E. all of the above are **TRUE**
8. Which of the following is/are **TRUE**?
- A. eye movements are absent in phasic REM sleep
  - B. eye movements are absent in stage 4 sleep
  - C. hypnic jerks occur in stage 1 sleep
  - D. the EEG of stage 1 sleep contains sleep spindles and K-complexes
  - E. two of the above are **TRUE**
9. Which of the following statements is **TRUE**?
- A. the EEG in REM sleep is similar to that of stage 1
  - B. theta waves are seen in stage 4 sleep
  - C. in the tonic phase of REM there are irregular bursts of rapid eye movements and muscle twitches
  - D. in the phasic phase of REM there is a generalized atonia of skeletal muscles except for the extraocular muscles and the diaphragm
  - E. eye movements occur in stage 4 sleep
10. When it comes to sleep, a healthy young medical student:
- A. spends most of his/her sleep in stage 1
  - B. spends most of his/her time in stage 2
  - C. has REM-NREM cycles that last about 60 minutes
  - D. has most of his/her slow wave sleep early in the morning
  - E. has most of his/her dreaming during the first REM cycle

11. Which of the following statements is **TRUE**?

- A. during tonic REM sleep there are brief surges in both sympathetic and parasympathetic activity, resulting in a high degree of autonomic instability
- B. the autonomic nervous system is relatively stable state during stage 4 sleep
- C. blood pressure, heart rate, and cardiac output increase during stage 4 sleep
- D. arrhythmias are most prevalent in stage 1 sleep
- E. temporary breathing instability and/or periodic breathing may occur in stage 4 sleep

12. Which of the following statements is **TRUE**?

- A. brain and body temperature are up-regulated during NREM sleep
- B. growth hormone is released primarily early in the morning
- C. prolactin peaks during the middle portion of the night
- D. thyroid stimulating hormone reaches its peak level in the morning, just prior to brushing your teeth
- E. sleep onset promotes cortisol release

13. Which of the following statements is/are **TRUE**?

- A. patients with obstructive sleep apnea exhibit increased levels of GH and prolactin
- B. sleep deprivation causes HPA axis activation in the evening of the day following deprivation (now here is a real “big picture” question-duh!!)
- C. John Harting naps less than Mark Carl Weston (FALSE!!!)
- D. REM sleep is accompanied by nocturnal penile tumescence and increased vaginal blood flow
- E. two of the above is **TRUE**

14. Which of the following nuclei/areas contain DA neurons?

- A. preoptic area
- B. anterior hypothalamus
- C. PPT
- D. reticularis pontis
- E. substantia nigra, pars compacta

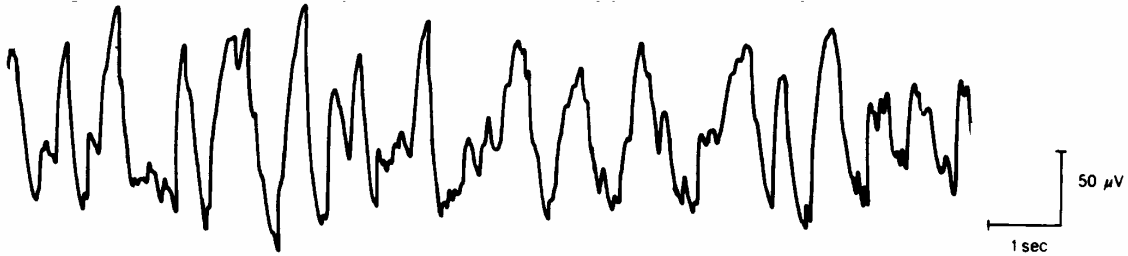
15. A complete transection of the brain stem at the level of the spino-medullary junction:

- A. will result in insomnia
- B. will result in a state of constant NREM sleep
- C. will result a complete absence of REM sleep
- D. will interrupt fibers ascending from reticularis pontis
- E. will have no effect on the EEG

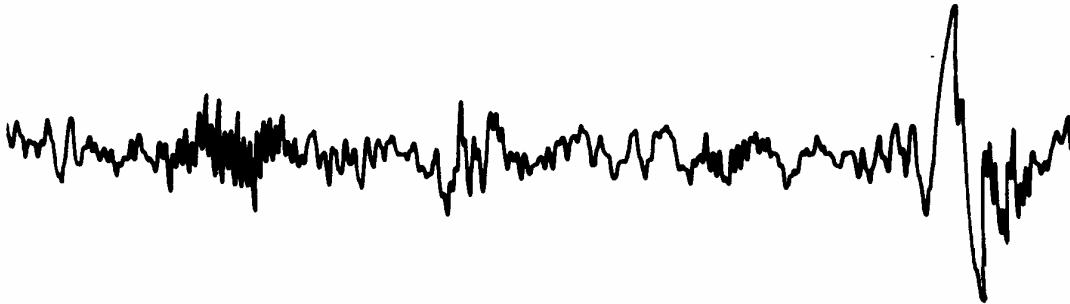
16. A lesion of the nucleus reticularis pontis:
- A. will result in insomnia
  - B. will interrupt descending input that **directly** innervates the spinal cord
  - C. will result a complete absence of REM sleep
  - D. will have no effect on the sleep wake cycle
  - E. will result in a flat EEG
17. Which of the following statements is/are **TRUE**?
- A. DA release is enhanced by amphetamine and cocaine and enhances wakefulness
  - B. ACh concentrations in the thalamus are lowest during wakefulness and REM sleep
  - C. nicotine decreases arousal
  - D. muscarinic receptor antagonists increase arousal
  - E. neostigmine decreases arousal
18. Which of the following statements is/are **TRUE**?
- A. antihistamines increase arousal
  - B. damage to the posterior hypothalamus, including the TM, results in somnolence (sleepy state)
  - C. serotonergic and noradrenergic neurons are most active during REM sleep
  - D. serotonergic and noradrenergic neurons excite cells in reticularis pontis
  - E. GABA plays no role in the transition between NREM and REM sleep
19. Sleep patterns in infants differ from those in adults in all of the following ways **EXCEPT**:
- A. infants sleep about twice as much as adults
  - B. the sleep of infants is spread across the day whereas adults show a diurnal pattern
  - C. infants spend less time in REM sleep
  - D. REM and NREM sleep cycle back and forth more rapidly in infants
  - E. the elderly nap more than MED 1s
20. All of the following may be associated with aging **EXCEPT**:
- A. loss of delta sleep
  - B. increased prevalence of sleep disorders
  - C. decreased total amounts of sleep
  - D. increased daytime napping
  - E. more wakefulness during the nocturnal sleep period

21. The human circadian pacemaker is located in the:
- A. supraoptic nucleus
  - B. pineal
  - C. pons
  - D. pituitary
  - E. suprachiasmatic nucleus
22. The period of the endogenous human circadian pacemaker using the temporal isolation protocol:
- A. approximately 24 hours
  - B. 25 hours
  - C. 23 hours
  - D. extremely variable
  - E. 12 hours
23. Which of the following statements is **TRUE**?
- A. REM occupies less of a one year-old girl's sleep than it does her mother's
  - B. there are approximately 90-100 minutes between NREM and REM sleep in human infants, while this interval is 50-60 minutes in adult humans
  - C. adolescents need less sleep than preadolescents
  - D. premature babies have less REM than those born at term
  - E. REM occupies about twenty to twenty five percent of total sleep in childhood and adulthood.
24. Which of the following statements is **TRUE**?
- A. stages 3 and 4 of NREM sleep show a steady increase across the lifespan
  - B. gender is the most important factor that determines how humans characteristically sleep
  - C. a newborn infant has less REM sleep than John Harting
  - D. the 24 hour total sleep time of John Harting is similar to MED 1s because he is able to nap in the back of 140 Bardeen during lecture, especially when his laser pointer doesn't work
  - E. John Harting gets more nocturnal sleep than MED 1s
25. Which of the following is/are **TRUE**?
- A. the amount of time in stages 1 and 2 NREM sleep decreases across the lifespan
  - B. narcolepsy is by far the most prevalent sleep disorder
  - C. periodic leg movements (or nocturnal myoclonus) and sleep apnea are more prevalent in children than the aged
  - D. Dean Farrell has more delta waves in his EEG when sleeping than MED1s
  - E. none of the above is **TRUE**

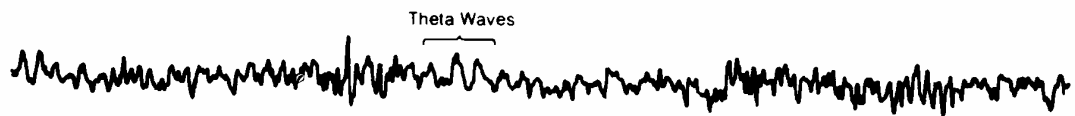
26. Which of the following statements is/are **TRUE**?
- A. the pacemaker for circadian rhythms lies in the supraoptic nucleus (SON)
  - B. the pacemaker for circadian rhythms lies in the suprachiasmatic nucleus (SCN)
  - C. sleep propensity is maximal at the peak of core body temperature
  - D. cell groups necessary for the generation of REM sleep are primarily in the midbrain (near the ruber)
  - E. a lesion of the SCN results in an animal that gets less total sleep each day
27. Which of the following statements is/are **TRUE** regarding a desynchronized EEG?
- A. occurs during delta sleep
  - B. high amplitude voltage
  - C. 2 cps (Hz)
  - D. low amplitude voltage
  - E. none of the above are **TRUE**
28. Which of the following statements is/are **TRUE** regarding a synchronized EEG?
- A. occurs during REM sleep
  - B. low amplitude
  - C. 2 cps (Hz)
  - D. present during attention
  - E. present while taking a neuro exam
29. Which of the following statements is **FALSE** regarding REM sleep?
- A. loss of muscle tone during tonic phase
  - B. referred to as “paradoxical sleep
  - C. percentage increases with age
  - D. is associated with dreaming
  - E. high frequency and low amplitude EEG pattern



30. Which of the following statements is **TRUE** regarding the EEG pattern shown above?
- A. the patient is alert
  - B. the EEG is asynchronous and low voltage
  - C. represents stage 1 sleep
  - D. is 8-12 cycles per second (cps)
  - E. represents delta or slow wave sleep



31. Which of the following statements is **TRUE** regarding the EEG pattern shown above?
- A. stage 4 sleep
  - B. stage 1 sleep
  - C. pattern seen during a neuro exam (sometimes?)
  - D. dominant pattern is 8-12 cps
  - E. sleep spindles and K complexes are present



32. Which of the following statements is **TRUE** regarding the EEG pattern shown above?
- A. very different from EEG seen during REM sleep
  - B. stage 4 sleep
  - C. 18-24 cps
  - D. EEG more asynchronous than in stage 4 sleep
  - E. sleep spindles and K complexes are present





33. Which of the following statements is **TRUE** regarding the EEG pattern shown above?

- A. very different from EEG during stage 1 sleep
- B. dreaming never occurs
- C. EEG is less asynchronous than in stage 4 sleep
- D. sleep spindles and K complexes are present
- E. muscle tone decreases during the tonic phase of this sleep

34. Hypocretin (orexin):

- A. inhibits the LC
- B. is released in greater amounts during sleep (maintains sleep)
- C. cells releasing it are normal in patients with narcolepsy
- D. is released from the thalamus
- E. is released from the hypothalamus

35. Which of the following statements is **TRUE**?

- A. process S increases during sleep
- B. process C reaches its peak around 10:00PM
- C. process S decreases the longer you are awake
- D. process S is responsible for nocturnal sleep onset
- E. none of the above are **TRUE**

**PROBLEM SOLVING ANSWERS**

1. A	11. B	21. A	31. E
2. E	12. C	22. B	32. D
3. E (C and D)	13. E (B and D)	23. E	33. E
4. B	14. E	24. D	34. E
5. E	15. E	25. E	35. D
6. E	16. C	26. B	
7. E	17. A	27. D	
8. E (B and C)	18. B	28. C	
9. A	19. C	29. C	
10. B	20. C	30. E	