Acknowledgement: Ganong medical Physiology

SLEEP STAGES

There are two kinds of sleep: rapid eye movement (REM) sleep and nonREM (NREM), or slow-wave sleep. REM sleep is so named because of the characteristic eye movements that occur during this stage of sleep. NREM sleep is divided into four stages (Figure 14–7). As a person begins to fall asleep and enters stage 1, the EEG shows a low-voltage, mixed fre- quency pattern. A theta rhythm (4–7 Hz) can be seen at this early stage of slow-wave sleep. Throughout NREM sleep, there is some activity of skeletal muscle but no eye move- ments occur. Stage 2 of NREM sleep is marked by the appear- ance of sinusoidal waves called sleep spindles (12–14 Hz) and occasional high voltage biphasic waves called K com-

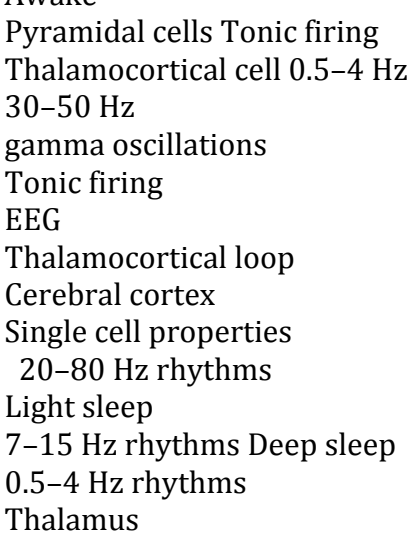

FIGURE 14−6 Correlation between behavioral states, EEG, and single-cell responses in the cerebral cortex and thalamus. The EEG is characterized by high-frequency oscillations in the awake state and low-frequency rhythms during sleep. Thalamic and cortical neurons can also show different patterns of rhythmic activity. Thalamocortical neurons show slow rhythmic oscillations during deep sleep, and fire tonic trains of action potentials in the

plexes. In stage 3 of NREM sleep, a high-amplitude delta rhythm (0.5–4 Hz) dominates the EEG waves. Maximum slowing with large waves is seen in stage 4 of NREM sleep. Thus, the characteristic of deep sleep is a pattern of rhythmic slow waves, indicating marked synchronization; it is some- times referred to as slow-wave sleep. While the occurrence of theta and delta rhythms is normal during sleep, their appear- ance during wakefulness is a sign of brain dysfunction.

Transition from sleep to waking

awake state. Most pyramidal neurons in the cortex generate only tonic trains of action potentials, although others may participate in the generation of high

frequency rhythms through activation of rhythmic bursts of spikes. The thalamus and cerebral cortex
are connected together in a loop. (Modified from McCormick DA: Are thalamocortical rhythms the Rosetta stone of a subset of neurological disorders? Nat Med 1999;5:1349.)

REM SLEEP

The high-amplitude slow waves seen in the EEG during sleep are periodically replaced by rapid, low-voltage EEG activity, which resembles that seen in the awake, aroused state and in stage 1 sleep (Figure 14–7). For this reason, REM sleep is also called paradoxical sleep. However, sleep is not interrupted; indeed, the threshold for arousal by sensory stimuli and by

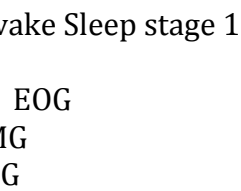

FIGURE 14–7 EEG and muscle activity during various stages of the sleep–wake cycle. NREM sleep has four stages. Stage 1 is characterized by a slight slowing of the EEG. Stage 2 has high-amplitude K complexes and spindles. Stages 3 and 4 have slow, high-amplitude delta waves. REM sleep is characterized
by eye movements, loss of muscle tone, and a low-amplitude, high-frequency activity pattern. The higher voltage activity in
the EOG tracings during stages 2 and 3 reflect high amplitude
EEG activity in the prefrontal areas rather than eye movements. EOG, electro-oculogram registering eye movements; EMG, electromyogram registering skeletal muscle activity. (Reproduced with permission from Rechtschaffen A, Kales A: A Manual of Standardized Terminology, Techniques and Scoring System and Sleep Stages of Human Subjects. Los Angeles: University of California Brain Information Service, 1968.)

stimulation of the reticular formation is elevated. Rapid, rov- ing movements of the eyes occur during paradoxical sleep, and it is for this reason that it is also called REM sleep. Another characteristic of REM sleep is the occurrence of large phasic potentials that originate in the cholinergic neurons in the pons and pass rapidly to the lateral geniculate body and from there to the occipital cortex. They are called pontogeniculo-occipital (PGO) spikes. The tone of the skeletal muscles in the neck is markedly reduced during REM sleep.

Humans aroused at a time when they show the EEG char- acteristics of REM sleep generally report that they were dream- ing, whereas individuals awakened from slow-wave sleep do not. This observation and other evidence indicate that REM sleep and dreaming are closely associated.

Positron emission tomography (PET) scans of humans in REM sleep show increased activity in the pontine area, amygdala, and anterior cingulate gyrus, but decreased activity in the prefrontal and parietal cortex. Activity in visual associa- tion areas is increased, but there is a decrease in the primary visual cortex. This is consistent with increased emotion and operation of a closed

neural system cut off from the areas that relate brain activity to the external world.

DISTRIBUTION OF SLEEP STAGES

In a typical night of sleep, a young adult first enters NREM sleep, passes through stages 1 and 2, and spends 70–100 min in stages 3 and 4. Sleep then lightens, and a REM period follows. This cycle is repeated at intervals of about 90 min throughout the night (Figure 14–8). The cycles are similar, though there is less stage 3 and 4 sleep and more REM sleep toward morning. Thus, 4–6 REM periods occur per night. REM sleep occupies 80% of total sleep time in premature infants and 50% in full- term neonates. Thereafter, the proportion of REM sleep falls rapidly and plateaus at about 25% until it falls to about 20% in the elderly. Children have more total sleep time (8–10 h) compared to most adults (about 6 h).

IMPORTANCE OF SLEEP

Sleep has persisted throughout evolution of mammals and birds, so it is likely that it is functionally important. Indeed, if humans are awakened every time they show REM sleep, then permitted to sleep without interruption, they show a great deal more than the normal amount of REM sleep for a few nights. Relatively prolonged REM deprivation does not seem to have adverse psychological effects. However, rats deprived of all sleep for long periods lose weight in spite of increased caloric intake and eventually die. Various studies imply that sleep is needed to maintain metabolic-caloric balance, thermal equi- librium, and immune competence.

In experimental animals, sleep is necessary for learning and memory consolidation. Learning sessions do not improve performance until a period of slow-wave or slow-wave plus REM sleep has occurred. Clinical Box 14–2 describes several common sleep disorders.

FIGURE 14–8 Normal sleep cycles at various ages. REM sleep is indicated by the darker colored areas. In a typical night of sleep, a young adult first enters NREM sleep, passes through stages 1 and 2, and spends 70–100 min in stages 3 and 4. Sleep then lightens, and a REM period follows. This cycle is repeated at intervals of about 90 min throughout the night. The cycles are similar, though there is less stage 3 and 4 sleep and more REM sleep toward morning. REM sleep occupies 50% of total sleep time in neonates; this proportion declines rapidly and plateaus at ~25% until it falls further in the elderly. (Reproduced with permission from Kales AM, Kales JD: Sleep disorders. N Engl J Med 1974;290:487.)

CLINICAL USES OF THE EEG

The EEG is sometimes of value in localizing pathologic pro- cesses. When a collection of fluid overlies a portion of the cor- tex, activity over this area may be damped. This fact may aid in diagnosing and localizing conditions such as subdural hema- tomas. Lesions in the cerebral cortex cause local formation of transient disturbances in brain activity, marked by high- voltage abnormal waves that can be recorded with an EEG. Seizure activity can occur because of increased firing of neu- rons that are excitatory (eg, release of glutamate) or decreased firing of neurons that are inhibitory (eg, release GABA).

Awake

REM 1 2 3 4
Awake
REM 1 2 3 4
Awake
REM 1 2 3 4
Children
1234567
Young Adults
1234567
Elderly
1234567 Hours of sleep
Sleep stages Sleep stages Sleep stages

276 SECTION II Central and Peripheral Neurophysiology
CLINICAL BOX 14–2
Sleep Disorders
Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally, and in which there is a sudden loss of voluntary muscle tone (cata- plexy), an eventual irresistible urge to sleep during daytime, and possibly also brief episodes of total paralysis at the beginning or end of sleep. Narcolepsy is characterized by a sudden onset of REM sleep, unlike normal sleep that begins with NREM, slow- wave sleep. The prevalence of narcolepsy ranges from 1 in 600 in Japan to 1 in 500,000 in Israel, with 1 in 1000 Americans being affected. Narcolepsy has a familial incidence strongly associated with a class II antigen of the major histocompatibility complex on chromosome 6 at the HLA-DR2 or HLA-DQW1 locus, imply- ing a genetic susceptibility to narcolepsy. The HLA complexes are interrelated genes that regulate the immune system (see Chapter 3). Compared to brains from healthy subjects, the brains of humans with narcolepsy often contain fewer hypocretin (orexin)-producing neurons in the hypothalamus. It is thought that the HLA complex may increase susceptibility to an immune attack on these neurons, leading to their degeneration.
Obstructive sleep apnea (OSA) is the most common cause of daytime sleepiness due to fragmented sleep at night and af- fects about 24% of middle-aged men and 9% of women in the United States. Breathing ceases for more than 10 s during fre- quent episodes of obstruction of the upper airway (especially the pharynx) due to reduction in muscle tone. The apnea causes brief arousals from sleep in order to reestablish upper airway tone. An individual with OSA typically begins to snore soon after falling asleep. The snoring gets progressively louder until it interrupted by an episode of apnea, which is then followed by a loud snort and gasp, as the individual tries to breathe. OSA is not associated with a reduction in total sleep time, but individuals with OSA ex- perience a much greater time in stage 1 NREM sleep (from an average of 10% of total sleep to 30–50%) and a marked reduction in slow-wave sleep (stages 3 and 4 NREM sleep). The pathophysi- ology of OSA includes both a reduction in neuromuscular tone at the onset of sleep and a change in the central respiratory drive.
Periodic limb movement disorder (PLMD) is a stereotypi- cal rhythmic extension of the big toe and dorsiflexion of the
TYPES OF SEIZURES

Epilepsy is a condition in which there are recurring, unpro- voked seizures that may result from damage to the brain. The seizures represent abnormal, highly synchronous neuronal activity. Epilepsy is a syndrome with multiple causes. In some forms, characteristic EEG patterns occur during seizures; between attacks; however, abnormalities are often difficult to demonstrate. Seizures are divided into partial (focal) seizures and generalized seizures.

Partial seizures originate in a small group of neurons and can result from head injury, brain infection, stroke, or tumor,

ankle and knee during sleep lasting for about 0.5–10 s and re- curring at intervals of 20–90 s. Movements can actually range from shallow, continual movement of the ankle or toes, to wild and strenuous kicking and flailing of the legs and arms. Elec- tromyograph (EMG) recordings show bursts of activity during the first hours of NREM sleep associated with brief EEG signs of arousal. The duration of stage 1 NREM sleep may be increased and that of stages 3 and 4 may be decreased compared to age- matched controls. PLMD is reported to occur in 5% of individu- als between the ages of 30 and 50 years and increases to 44% of those over the age of 65. PLMD is similar to restless leg syn- drome in which individuals have an irresistible urge to move their legs while at rest all day long.

Sleepwalking (somnambulism), bed-wetting (nocturnal enuresis), and night terrors are referred to as parasomnias, which are sleep disorders associated with arousal from NREM and REM sleep. Episodes of sleepwalking are more common in children than in adults and occur predominantly in males. They may last several minutes. Somnambulists walk with their eyes open and avoid obstacles, but when awakened they cannot re- call the episodes.

THERAPEUTIC HIGHLIGHTS

Excessive daytime sleepiness in patients with narcolepsy can be treated with amphetamine-like stimulants, includ- ing modafinil, methylphenidate (Ritalin), and meth- amphetamine. Gamma hydroxybutyrate (GHB) is used to reduce the frequency of cataplexy attacks and the inci- dences of daytime sleepiness. Cataplexy is often treated with antidepressants such as imipramine and desipra- mine, but these drugs are not officially approved by the US Federal Drug Administration for such use. The most common treatment for OSA is continuous positive air- flow pressure (CPAP), a machine that increases airway pressure to prevent airway collapse. Drugs have generally proven to have little or no benefit in treating OSA. Drugs used to treat Parkinson disease, dopamine agonists, can be used to treat PLMD.

but often the cause is unknown. Symptoms depend on the sei- zure focus. They are further subdivided into simple partial seizures (without loss of consciousness) and complex partial seizures (with altered consciousness). An example of a simple partial seizure is localized jerking movements in one hand progressing to clonic movements of the entire arm lasting about 60–90 s. Auras typically precede the onset of a partial seizure and include abnormal sensations. The time after the seizure until normal neurological function returns is called the postictal period.

Generalized seizures are associated with widespread elec- trical activity and involve both hemispheres simultaneously.