Section 1 – Normal sleep

Introduction: the basic neurology of sleep

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Overview

Sleep is not an inactive state.

Dating back to early modern classifications of sleep based on electrophysiological measurements, the inherent activities of various neural substrates in sleep have been readily recognized.

Normal sleep has been classified as having two characteristic divisions: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. These sleep states are defined by neurophysiological parameters of electroencephalogram (EEG), electrooculogram (EOG), and surface electromyogram (EMG), as detailed by Dr. Billiard in the following chapter. These characteristics clearly distinguish the NREM and REM sleep states from the wakefulness state.

Behaviorally, sleep is a reversible state characterized by perceptual disengagement and apparent unresponsiveness to the environment with closed eyes, reduced movements, and recumbency. Early behaviorally based studies revealed that even in those with unequivocal electrophysiologic correlates of being asleep, arousal to one's own name and responsiveness to other auditory stimuli persist.

Additionally, the understanding that continues to evolve of the neurophysiology and neurochemistry of normal sleep suggests that many of the neurologic substrates involved are by no means passive, but rather very active in sleep. An example is the increase in cerebral blood flow that occurs in normal sleep. Both animal and human studies have shown that cerebral blood flow in NREM sleep may increase up to 25% greater than in wakefulness, and up to 80% greater in REM sleep. These changes in cerebral blood flow, at least in part, correlate with concomitant increased brain oxygen metabolism in sleep.

Wakefulness

In the late nineteenth century and early twentieth century, it was posited that a sleep/wake center existed in the midbrain and caudal diencephalon, based on clinical correlates of nervous system lesions. The ascending reticular activating system was defined as a center point in maintenance of wakefulness in a series of sophisticated

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animal studies. Electrical stimulation of the reticular formation in the brainstem of anesthetized cats resulted in cortical activation and EEG low-voltage fast activity. Lesions of the brainstem reticular formations, especially in midbrain tegmentum and oral pontine nuclei, resulted in EEG changes similar to sleep. Further studies revealed that the reticular formation receives collateral input from visceral, somatic, and special sensory systems, and projects ascending pathways to the forebrain by way of a dorsal path to the thalamus and a ventral projection through the hypothalamus, subthalamus, and ventral thalamus to the basal forebrain. An important role of the hypothalamus was suggested in *cerveau isolé* studies, and further clarified in subsequent animal studies with localization to the posterior hypothalamus.

Catecholamines are central to wakefulness. Levodopa may stimulate cortical activation and prolonged arousal but has also been reported to induce sleep in specific instances, and a biphasic effect of dopamine agonists on sleep and wakefulness has been described in animals. Amphetamines, which release dopamine and norepinephrine, also produce arousal and prolonged vigilance. Dopaminergic neurons are present in the substantia nigra, the midbrain ventral tegmentum, the posterior hypothalamus, and the subthalamus. Norepinephrine-containing neurons are most concentrated in the dorsolateral pontine tegmentum locus ceruleus and in the pontine and medullary reticular formation, projecting to the entire forebrain and all areas of the cortex.

Cholinergic contributions to cortical activation and wakefulness have been described. Both muscarinic and nicotinic cholinergic agonists can activate wakefulness. Cholinergic neurons in the caudal mesencephalic and oral pontine reticular formation project to the basal forebrain, thalamus, lateral hypothalamus, and frontal cortex, with cholinergic neurons also concentrated in the basal forebrain. Cortical activation and wakefulness have been associated with acetylcholine release in the cortex.

Histamine may have an effect on arousal, as may glutamate. Substance P and other peptides may be contributors to wakefulness. The understanding of the importance of the hypocretinergic hypothalamic system in wakefulness and in sleep/wake state control mechanisms continues to evolve.

NREM sleep

With the knowledge of the activating systems involved in wakefulness, there was a supposition early last century that sleep may be a result of inactivity of the wake-promoting pathways, that is, sleep as a passive state. Animal studies involving brainstem transsection at the oral pontine tegmentum, however, resulted in complete insomnia, connoting that sleep is an active state generated by structures in the lower brainstem. The concept of active sleep-generating structures was further supported in cat studies in which insomnia resulted from lesions of the raphe system from the medulla to the pontomesencephalic border, and from electrical stimulation of the solitary tract nucleus and dorsal reticular formation producing EEG cortical synchronization suggestive of NREM sleep. Indirect evidence of similar structures in humans is seen in reports of reduction or abatement of NREM sleep in raphe nucleus infarction and in other brainstem lesions.

Thalamic nucleus reticularis, to which projections arise from the midbrain reticular system, has been elegantly demonstrated to be the generator of NREM sleep spindle activity in the thalamic nuclei and in cortical projections.

Hypothalamic sleep synchrony centers, as well as wake centers, were implied in the *cerveau isolé* studies of Bremer in the 1930s. Anterior hypothalamic localization in humans as a sleep facilitatory center, in contradistinction to posterior hypothalamic wake centers, was proposed by Von Economo. Electrical stimulation studies in the cat of the preoptic area and basal forebrain resulted in synchronized NREM sleep. Thus the anterior hypothalamus, preoptic area, and basal forebrain, in conjunction with brainstem reticular formation, appear to be central to generation of NREM sleep. Additionally, recent work has shown that the amygdala may also, in part, be related to NREM sleep.

Serotonin appears to have a role in the induction of NREM sleep, as demonstrated in reserpine studies nearly 50 years ago. Blocking of serotonin either pharmacologically or by lesions of raphe serotonin nuclei leads to severe insomnia in animal studies, which is reversible by reinstituting serotonin. Similar restoration of NREM sleep in humans by administration of the serotonin precursor 5-hydroxytryptamine in a severe case of insomnia has been reported. Single unit recordings have shown that raphe neurons reduce firing with NREM sleep and cease firing in REM sleep. This has led to the conclusion that serotonergic neurons facilitate NREM sleep onset, but are not singularly essential for the occurrence of NREM sleep.

Adenosine may contribute to NREM sleep in that caffeine, which blocks adenosine receptors, can block NREM sleep. Adenosine release in the basal forebrain in NREM sleep has been demonstrated. A model of adenosine contributing to sleep/wake homeostatic regulation has been proposed. There is an evolving understanding of the importance of the interactions of adenosine, basal forebrain cholinergic cell groups, and numerous central nervous system sites in sleep homeostasis. Gamma-aminobutyric acid (GABA) may also play a role in NREM sleep synchrony.

REM sleep

Rapid eye movement (REM) sleep is characterized by desynchronized low-voltage EEG patterns, in contradistinction to the synchronized EEG of NREM sleep. In addition, REM sleep also is characterized by skeletal muscle atonia.

Episodic bursts of rapid eye movements, which are at times concurrent with transitory muscle activity and cardiorespiratory changes, are an additional hallmark of REM sleep. Interestingly, though the REM sleep cortical EEG is desynchronized, depth electrode studies in the cat reveal highly synchronized theta rhythm in the hippocampus, and also subcortically the presence of ponto-geniculo-occipital (PGO) phasic spikes.

In investigating where REM sleep is generated, transection between the midbrain and pons in the cat resulted in absence of REM sleep characteristics rostrally but maintenance of REM sleep caudally, indicating that the neural structures important to REM sleep generation must be located caudal to this transection.

In humans, high cervical lesions interrupting continuity between the medulla and spinal cord have been shown to disrupt spinal innervated REM atonia, but to preserve other characteristics of REM sleep, thus further localizing the neural structures generating REM sleep to rostral to the spinal cord, but caudal to the midbrain.

When transection studies were completed in cats between the medulla and pons, caudal medullary cycles of activated and quiescent states, respectively similar to wakefulness and NREM sleep, were seen. Rostral to the transection three states were seen, similar to wakefulness, NREM sleep, and REM sleep. Thus the pons is central in generating the characteristics of REM sleep. Additional investigations localized REM sleep-generating phenomena to the lateral region of the reticularis pontis oralis lateral to the locus ceruleus. Further, atonia can be elicited in the medial medulla at the nucleus reticularis magnocellularis. Recordings of cellular unit firing in the lateral pontine reticular formation and medial medulla have revealed very high discharges in REM sleep and minimal to no firing in NREM sleep or wakefulness. These cells have been described as REM "sleep-on" cells and are present in the lateral pons, with projections to the medial medulla. The amygdala may also be modulatory or contributory to REM sleep.

Acetylcholine appears to be important in REM sleep components. Acetylcholine depletion reduces EEG desynchronization and REM sleep. Acetylcholinesterase inhibitors increased some REM sleep characteristics. The lateral pontine REM "sleep-on" cells are cholinoceptive. Injection of cholinomimetics into the pontine tegmentum in cats resulted in atonia, rapid eye movements, and PGO spikes. Though acetylcholine may not be the exclusive neurochemical component of REM sleep, it does appear to contribute to EEG desynchrony, muscle atonia, and PGO spikes.

Serotonergic cells of the midline raphe system and noradrenergic cells of the locus ceruleus may have a role in gating, inhibiting, or disinhibiting some aspects of REM sleep. This raises the possibility of a reciprocal interaction of REM "sleep-off" cells in these systems, though the relation is not absolute. A recent study using microinjection into pedunculopontine tegmentum of norepinephrine, serotonin, and adenosine in the rat did not suppress REM sleep, which will further prompt revisiting of the reciprocal interaction model.

Conclusion

Though there clearly appears to be a biological requirement for sleep, the physiological role of sleep remains unclear. Ongoing investigations and sleep research continue to move forward, and we await exciting developments that will help solve the many questions yet to be answered.

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American Academy of Sleep Medicine. www.aasmnet.org.

1 Normal sleep

Michel Billiard

Introduction

The state of wakefulness regularly alternates with the states of sleep. Our initial know-ledge of the states of sleep was based on observations of individual subjects while asleep. The beginning of the scientific era of research in normal humans dates back to the sleep deprivation studies conducted by Kleitman in the 1920s. In the following decade, the first classification of sleep stages was published by Loomis *et al.* in 1937, and Kleitman's comprehensive landmark monograph *Sleep and Wakefulness* was published in 1939. Loomis's classification was based on electroencephalographic (EEG) criteria alone and distinguished five different sleep states, from wakefulness (A) to deep sleep (E). In 1953, Aserinsky and Kleitman described a special type of sleep with rapid eye movements, and sleep was subsequently classified based on EEG and electrooculographic (EOG) para-meters. This classification system distinguished four stages of sleep without rapid eye movements (NREM sleep) and a state of sleep with rapid eye movements (REM sleep). Following the discovery of muscle atonia accompanying REM sleep by Jouvet in 1962, a revised classification of sleep was developed using the three parameters of EEG, EOG, and electromyography (EMG). In 1968 this staging system was published in the *Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*, under the leadership of Rechtschaffen and Kales, and is still used worldwide.

Polysomnography

Polysomnography (PSG) is the recording of several electrophysiologic signals during sleep. Polysomnography uses the 10–20 international electrode placement system for EEG recording (Fig. 1.1). The minimum monitoring requires one EEG lead with electrode positions at either C3–A2 or C4–A1. It is standard practice to add a frontal electrode, most commonly F2. To record eye movements, electrodes are placed on the skin at the outer canthus of both eyes. The electrodes are placed so that eye movements result in signals going in the opposite direction, and head movements or EEG artifacts are recorded as signals going in the same directions. The electromyo-gram of the chin muscles is monitored with two electrodes placed under the chin. In order to obtain reliable identification of sleep stages, three EEG, two EOG, and one EMG channels are necessary. An electrocardiographic channel is mandatory, with
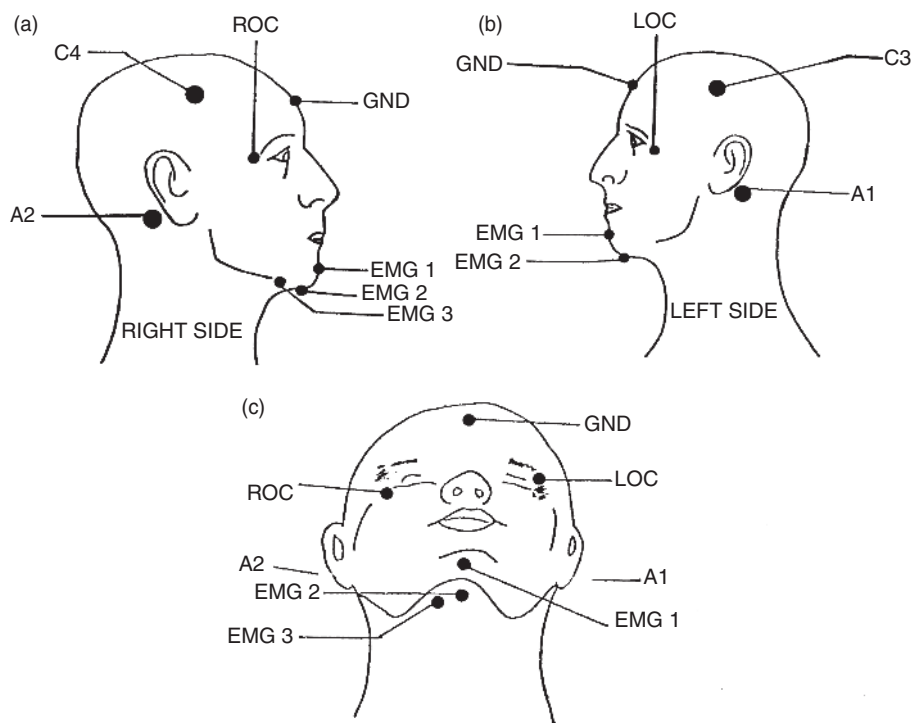
Fig. 1.1. Diagrammatic representation of electrode placements for recording the electrophysiologic phenomena of sleep. GND, ground electrode.

electrodes usually placed on the right shoulder and left leg. In a standard montage, leg muscles and respiration are monitored. The electrode placement for leg EMG is on the skin above right and left anterior tibialis muscles. Respiration is monitored by different methods. The most common montage comprises a nasal cannula/pressure transducer system, a mouth thermistor, a neck microphone, a thoracic and an abdominal band, and a pulse oximeter. Depending on the reason for the test, other variables may be added. The most common additions are esophageal pressure measurement, pulse transit time, body temperature, and additional EEG leads.

The signals obtained from these sensors are amplified and recorded on special systems. A minimum of 16 channels is recommended. The recording of sleep must be accompanied by a video recording of the sleeping subject, which can be synchronized with the polysomnographic recording. The frequency of sampling is important. The normal frequency is 128 cycles/second (Hz), although frequencies up to 500 Hz are used when doing a spectral analysis. Of note, most of the variables collected during sleep are qualitative or semi-quantitative at best.

Conventional analysis of wakefulness and sleep
Sleep macrostructure
Sleep is generally scored in 20- or 30-second segments or epochs. The scoring is performed using two international scoring systems. The Rechtschaffen and Kales