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Brain mechanisms that control sleep and waking

Published online: 2 July 2004
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Abstract This review paper presents a brief historical survey of the technological and early research that laid the groundwork for recent advances in sleep–waking research. A major advance in this field occurred shortly after the end of World War II with the discovery of the ascending reticular activating system (ARAS) as the neural source in the brain stem of the waking state. Subsequent research showed that the brain stem activating system produced cortical arousal via two pathways: a dorsal route through the thalamus and a ventral route through the hypothalamus and basal forebrain. The nuclei, pathways, and neurotransmitters that comprise the multiple components of these arousal systems are described. Sleep is now recognized as being composed of two very different states: rapid eye movements (REMs) sleep and non-REM sleep. The major findings on the neural mechanisms that control these two sleep states are presented. This review ends with a discussion of two current views on the function of sleep: to maintain the integrity of the immune system and to enhance memory consolidation.

Historical background

Three advances in technology and a clinical research finding during the first half of the twentieth century were critical for laying a foundation for the scientific advances that were generated in the latter half of the twentieth century.

This article is based in part on material in the book “The neural control of sleep and waking” (J. Siegel, 2002).

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Electroencephalography

The single most important tool for the scientific study of sleep and waking has been the electroencephalograph. This instrument records electrical activity of the brain and provides an objective measure of the state of the brain and the states of consciousness. Hans Berger in Jena, Germany, is credited with developing the first instrument that recorded electrical activity generated by the human brain. Berger, in 1925, had access to one of the first vacuum tube amplifiers manufactured by the Siemens Company and used this sensitive galvanometer to record the electrical activity from his young son’s brain. This landmark electroencephalographic (EEG) recording was published by Berger in 1929 (Berger 1929). This important advance was built upon earlier research with animals that demonstrated the electrical nature of neural activity (Brazier 1961).

Berger’s early work showed a clear EEG difference between sleep and waking. Research conducted 24 years later (Aserinsky and Kleitman 1953), showed that the EEG during sleep could be differentiated into at least two categories. One type of sleep was found to be associated with the occurrence of dreams and the other with non-dream sleep. Since dream sleep was found to be accompanied by episodes of rapid eye movement (REM), this state is often called REM sleep. Non-dream sleep is also called non-REM sleep. Figure 1a shows examples of EEG tracings during waking and during different stages of sleep.

An awake record is characterized by EEG waves that are low voltage (5–50 μ V) and high frequency (20–40 Hz) relative to voltages and frequencies seen during non-REM sleep. When a person falls asleep, a brief transitional state between waking and sleep is characterized by an EEG that resembles waking. During this period, recordings from electrodes placed on the skin around the eyes show the presence of sporadic slow eye movements. This transitional state is referred to as stage 1 sleep. As the individual progresses toward deeper sleep, stages 2, 3, and 4, the EEG shows higher amplitudes and lower frequencies.

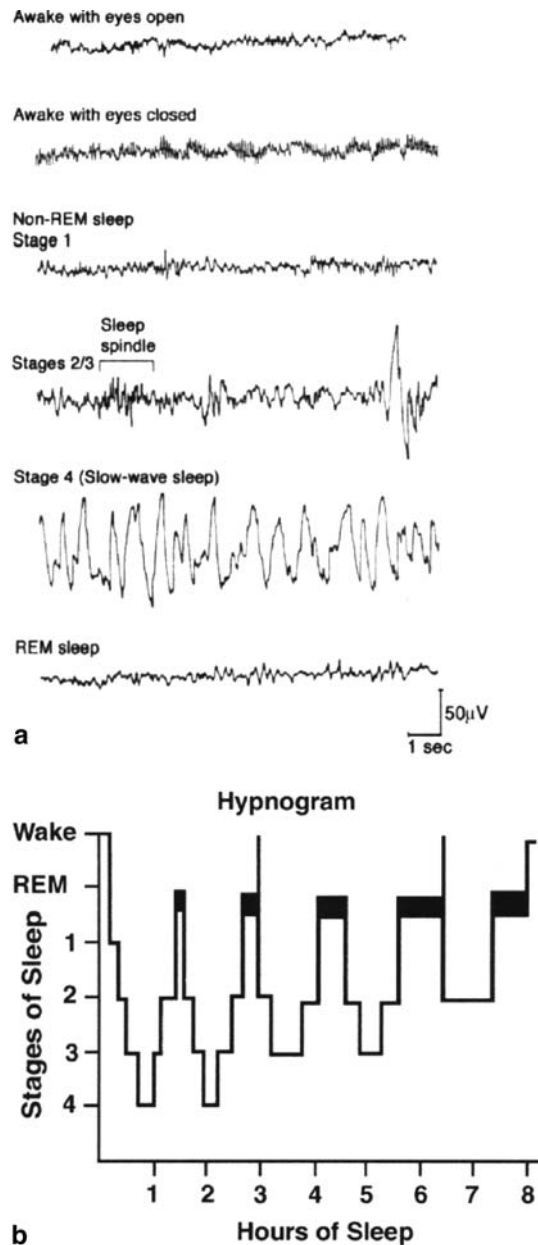


Fig. 1 **a** Examples of typical EEG recordings during waking and the different stages of sleep [reproduced from Purves et al. (1997) with the permission of Sinauer Associates, Sunderland, Mass.]. **b** A typical hypnogram which illustrates the progression of sleep stages as they cycle through an 8-h period of sleep. This graph shows that the deeper stages of non-REM sleep occur during the first half of the night and the durations of REM sleep increase during the course of the night [reproduced with permission from Siegel (2002) with the permission of Springer-Verlag, New York]

The deepest stage of non-dream sleep (stage 4 sleep) exhibits the highest amplitudes (100–400 μV) and lowest frequencies (0.5–3 Hz). Stages 3 and 4 are often referred to as slow-wave or high-voltage sleep. When the person enters a dream state, during which REMs occur, the EEG rapidly shifts from the slow-wave pattern to a pattern that resembles a waking and stage 1 sleep record. In addition to the low-voltage, high-frequency EEG seen during

waking, there are higher amplitude and slower frequency components in the 4–7 Hz range. This sleep state is often called low-voltage, REM, or dream sleep. Since the person is clearly asleep, but paradoxically the EEG looks like that of an awake person, this state is also referred to as paradoxical sleep.

Slow-wave sleep followed by a REM sleep episode is a pattern that repeats throughout the night. Each cycle of non-REM sleep followed by a REM episode is about 90 min in duration and typically yields five sleep cycles in an 8 h sleep period. Figure 1b is a hypnogram that graphically summarizes the sleep stages during a typical night's sleep.

The stereotaxic instrument

Electrical recordings that are most accessible from the brain and that are most revealing of the states of sleep and waking are from the cortical surface of the brain. However, the state of the cerebral cortex is not controlled by the cortex itself; it is controlled by structures below the cortical surface that cannot be approached under direct visual control. The stereotaxic instrument permits probes to be accurately inserted into the brain to experimentally manipulate deep structures and thus determine their influence on sleep and waking. Such manipulations include lesions to destroy neural tissue, electrical stimulation, and the application of chemicals. The first such device to be widely used was developed in London, England in the early 1900s by two neurosurgeons, Victor Horsley and Robert Clarke (Clarke and Horsley 1906; Marshall and Magoun 1990, 1991).

The stereotaxic instrument fixes the head in a standard orientation with respect to a probe drive and attached probe that can be moved above the skull and brain in the anterior–posterior (front-to-back) and medial–lateral (left and right) dimensions. The probe can then be lowered in the vertical dimension through a hole in the skull into the brain. Clarke and a collaborator developed an atlas of the human brain with plates that corresponded to the sagittal plane of the Horsley–Clarke stereotaxic instrument. The instrument in conjunction with the atlas permitted a probe to be positioned with considerable accuracy to a target deep within the brain. The subsequent development of stereotaxic instruments and brain atlases of different animal species was a great resource for brain research in general and for sleep–waking research in particular.

The cathode ray oscilloscope

The third technological advance that furthered understanding of the neural control of sleep and waking was the cathode ray tube. This device was necessary to explore the electrical activity of the brain at the single cell level. The voltage change of a single active brain cell (the action potential) occurs on the order of 1–3 ms. An electromechanical galvanometer, like an EEG-type recorder, does

not have a response time capable of tracking such a rapid voltage change. The electron beam of a cathode ray tube has virtually no inertia and can respond with millisecond and submillisecond speeds. When a microelectrode probe is placed within or near a nerve cell, the neural signal from that single neuron can be amplified and fed into a cathode ray oscilloscope and deflect its beam as the cell fires its action potential.

Two early pioneers of this technology were Joseph Erlanger and Herbert Gasser in St. Louis, Missouri in 1922. They recorded the compound action potential of whole nerves that contained the axonal processes of many nerve cells (Gasser and Erlanger 1922; Erlanger and Gasser 1924). The technique was soon applied, using fine-tipped microelectrodes, to the recording of single nerve cell action potentials. This approach permitted the discovery of neural events at the cellular level that occur during sleep and waking.

Encephalitis lethargica

A number of findings prior to the modern era of sleep-waking research were important, but the one advance that provided the first knowledge of brain regions central to sleep and waking occurred during the final years of World War I. During the period 1917–1919, a worldwide influenza epidemic produced an enormous number of fatalities. An estimated 25–40 million people died from what was commonly called the Spanish Flu.

Constantin von Economo, a psychiatrist and neurologist at the University of Vienna, saw a number of patients who had contracted the virus and exhibited symptoms of a variant of the disease that caused a sleep coma. This form of the disease was called encephalitis lethargica and was usually fatal. Von Economo, also a skilled neurohistologist, analyzed the brains of these patients and discovered the area that was severely damaged and caused the fatal sleep coma. His histology, utilizing a stain selective for cell bodies, revealed a profound loss of cells in the posterior hypothalamus and adjacent region of the mesencephalic reticular formation. This was the first evidence that these structures were necessary to maintain the waking state. Recent evidence suggests that the selective brain cell damage was caused not by an influenza virus but was due to an autoimmune disorder (Dale et al. 2004).

Another population of patients showed the opposite symptoms, namely an inability to sleep. Brain histology revealed a loss of cells in the anterior hypothalamus and the adjacent preoptic area of the basal forebrain. This was evidence for a brain region that is critical for the ability to sleep.

These findings, published in a series of papers beginning in 1923 (von Economo 1923, 1930) provided the first evidence of brain structures that are important for waking, the posterior hypothalamus and anterior reticular formation, and structures important for sleep, the anterior hypothalamus and preoptic area. Figure 2 is a schematic drawing of the cat brain that shows the locations of these

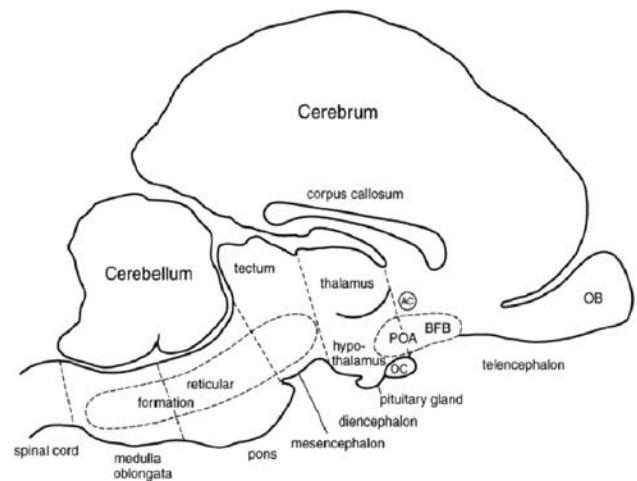


Fig. 2 Drawing of a cat brain based on a sagittal section close to the midline. This view shows the location of the reticular formation and other brain structures. Also represented are the boundaries (dashed lines) that demarcate the five subdivisions of the brain: the medulla oblongata and pons (hindbrain), the mesencephalon (mid-brain), and the diencephalon and telencephalon (forebrain). Abbreviations: AC anterior commissure, BFB basal forebrain, OB olfactory bulb, OC optic chiasm, POA preoptic area [reproduced with permission from Siegel (2002) with the permission of Springer-Verlag, New York]

regions of the brain. Figure 2 also shows the demarcations between the major subdivisions of the brain: the medulla oblongata, pons, and mesencephalon, which comprise the brain stem; and the diencephalon and telencephalon, which comprise the forebrain.

The neural structures and pathways for arousal

Shortly after the end of World War II, Giuseppe Moruzzi of the University of Pisa in Italy and Horace Magoun of Northwestern University in Illinois collaborated on a study conducted in Magoun's laboratory. They electrically stimulated the mesencephalic reticular formation of cats when the EEG recorded from the cerebral cortex signified a sleep-like state. Upon the onset of stimulation there was a rapid and dramatic change of the EEG to that of an awake brain (Moruzzi and Magoun 1949). Figure 3 from their landmark paper shows the EEG activation produced by the reticular formation stimulation. Subsequent work showed that destruction of the area stimulated by Moruzzi and Magoun produced animals with constant sleep-like behavior and EEG records (Lindsley et al. 1949, 1950; French et al. 1952). These findings were experimental confirmations of von Economo's clinical observations that damage to the reticular formation in encephalitis lethargica patients abolished the waking state. Based on these findings, the reticular formation in the rostral region of the brain stem and the neural pathways basic to the cortical arousal response became known as the ascending reticular activating system (ARAS). This concept has remained central in the sleep-waking field.

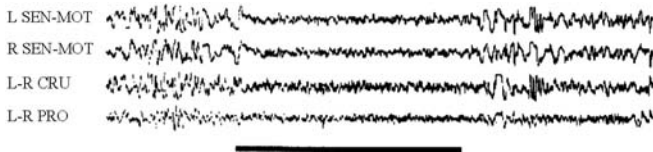


Fig. 3 Activation of the cerebral cortex by electrical stimulation of the reticular formation in the cat. This figure, from Moruzzi and Magoun's original paper of 1949, shows four channels of EEG cortical recordings during a period of high-voltage slow waves, characteristic of sleep. The horizontal line below the bottom EEG tracing marks the duration of stimulation to the reticular formation. It is readily seen that the reticular stimulation abruptly changed the cortical EEG from that of a sleep record to that of waking. At the offset of stimulation, with the reticular activating influence removed, the EEG returned to the slow waves of sleep [adapted from Moruzzi and Magoun (1949) with the permission of Elsevier Science, Amsterdam]

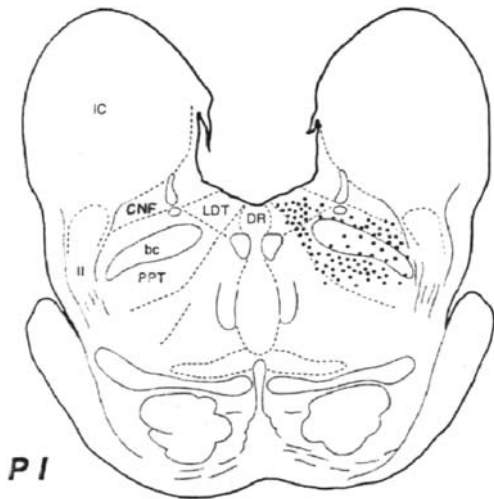


Fig. 4 A drawing of a frontal section through the brain stem of a cat showing the location of the peribrachial nuclei. The solid circles on the right represent cells of the ascending arousal system that synthesize and release acetylcholine. Abbreviations: bc brachium conjunctivum, CNF cuneiform nucleus, DR dorsal raphe nucleus, IC inferior colliculus, LDT laterodorsal tegmental nucleus, II lateral lemniscus, PPT pedunclopontine tegmental nucleus [adapted from Jones and Beaudet (1987) with the permission of Wiley-Liss, New York]

Subsequent to the pioneering work of Moruzzi and Magoun, research has revealed the specific nuclei and cell types of the reticular formation that produce cortical arousal. Coursing through the pontine and mesencephalic brain stem is a prominent fiber tract, the brachium conjunctivum, which carries signals from the cerebellum to the thalamus. Surrounding this fiber tract at the level of the pontine–mesencephalic junction are two nuclei, the pedunclopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT). The two nuclei are called the peribrachial nuclei. Using immunohistochemical techniques, Jones and Beaudet (1987) have shown that these nuclei contain acetylcholine-synthesizing neurons. These are the major cells of the ascending arousal system. Figure 4 shows the location of the peribrachial nuclei of the cat brain and the cholinergic cells located there.

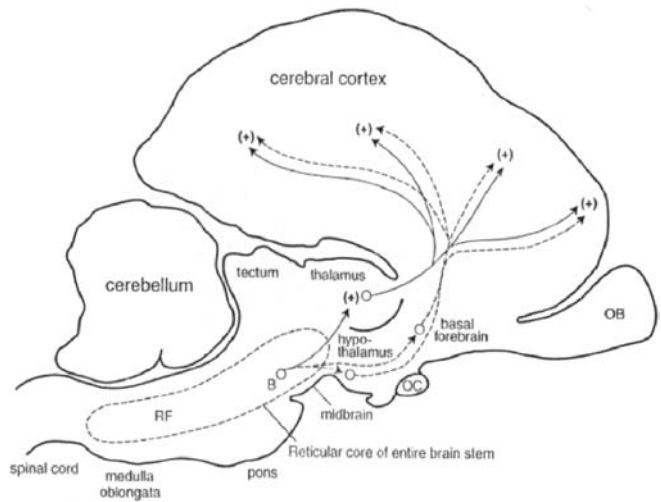


Fig. 5 The nuclei and pathways of the dorsal and ventral components of the ascending activating system that originate in cholinergic cells of the reticular formation. The dorsal pathway, represented by solid lines, activates the cortex via the thalamus. The ventral pathway (dashed lines) shows the involvement of the hypothalamus and basal forebrain in cortical activation. Abbreviations: OB olfactory bulb, OC optic chiasm, RF reticular formation [adapted from Jones (2000) with the permission of WB Saunders, Philadelphia]

Using a variety of neuroanatomical tracing techniques, cortical arousal from activation of the peribrachial nuclei is now known to be mediated by two routes: a dorsal and a ventral pathway. Figure 5 is a schematic representation of the nuclei and fiber tracts of these two pathways. The dorsal pathway is fairly direct. Peribrachial cells project to a group of nuclei named for their location in the thalamus: the midline and intralaminar nuclei of the thalamus. These nuclei project to broad areas of the cortex (Nauta and Kuypers 1958; Saper and Loewy 1980; Macchi and Bentivoglio 1986) and are often referred to as the non-specific or diffuse projection nuclei of the thalamus. When activated, the terminals of these fibers release glutamate, an excitatory amino acid neurotransmitter, and produce an arousal of the entire cerebral cortex.

The ventral pathway takes a more complex route to the cortex. Prior to reaching the thalamus, components of the tract from the reticular formation diverge from the dorsal bundle and course into and through the ventral region of the forebrain. The ventral pathway has been described by Jones (1993, 2000). In the ventral diencephalon, these fibers synapse upon cells of the tuberomammillary nucleus of the posterior hypothalamus. Cells of this hypothalamic nucleus project to the entire cerebral cortex and release histamine at their terminals. Histamine, a novel transmitter in the brain found only in these cells, has a strong arousal effect upon the cerebral cortex (Lin et al. 1988; Saper 1985, 1987).

Another population of cells recently discovered in the hypothalamus utilizes a peptide neurotransmitter called orexin or hypocretin. These cells also project to the cerebral cortex and produce arousal (Kilduff and Peyron 2000; Moore et al. 2001; Peyron et al. 1998). The popu-

lations of hypocretin and histamine neurons are both located in the posterior hypothalamus (Hopkins et al. 2001) and appear to innervate each other and cooperate to regulate arousal (Eriksson et al. 2001).

The ventral pathway from the cholinergic reticular formation continues more rostrally into the basal forebrain to terminate in cells that also synthesize acetylcholine. These basal forebrain cholinergic neurons project to a number of regions including the cerebral cortex and contribute to cortical arousal. The two components of the ventral pathway, the hypothalamus and basal forebrain, are shown in Fig. 5.

It appears that cortical arousal has its main control in cholinergic cells of the reticular formation. This brain stem influence is mediated by the dorsal (thalamic) and ventral (hypothalamic and basal forebrain) pathways that utilize their own neurotransmitters to activate the cortex, namely, glutamate, histamine, hypocretin, and acetylcholine. In addition, other brain stem nuclei provide serotonergic, noradrenergic, and dopaminergic influences to the cortex that modulate the sleep and waking states (Saper 1987).

The fact that there are multiple pathways and neurotransmitters that control cortical arousal helps us understand a clinical phenomenon. After various types of brain damage that cause a sleep-like coma, there is often some degree of recovery of function. This may be due to the multiple and somewhat redundant nature of the neural pathways that contribute to arousal.

The neural control of non-REM sleep

Evidence has accumulated that non-REM or slow-wave sleep is produced by inhibition of one or more of the influences that produce arousal. Electrical stimulation to a number of brain structures will produce the electrographic signs of sleep and, in behaving animals, behavioral sleep. In a series of experiments, Siegel and colleagues (Siegel and Lineberry 1968; Lineberry and Siegel 1971; Siegel and Wang 1974) showed that sleep-inducing stimulation that produced EEG slow waves recorded from the cerebral cortex, produced at the same time an alteration of the firing pattern of cells in the brain stem reticular activating system. Cells of the reticular formation typically underwent a decreased firing rate and, in some cases, a complete cessation of neural activity. After the sleep-inducing stimulation was terminated, there was a gradual recovery of firing in brain stem neurons as the cortical EEG slow waves shifted to a low-voltage waking record. This finding suggests that a sleep-inducing influence has its effect by inhibiting the neural activity of the reticular activating system.

The basal forebrain area, as described above, is involved in producing arousal. However, early experiments had shown quite convincingly that stimulation of this region in cats produced the EEG and behavioral signs of sleep (Serman and Clemente 1962a, 1962b). Later work, as described by Jones (1993) and Saper et al. (1997),

showed that the basal forebrain cholinergic cells that project to the cortex mediate the basal forebrain-produced arousal. In addition, the basal forebrain was shown to also house neurons that synthesize and release gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. One target of these cells is the histaminergic neurons of the posterior hypothalamus. It appears that the sleep-inducing effect of basal forebrain stimulation is not directly on the cortex, but is mediated by the inhibitory effect of GABA on the hypothalamic component of the arousal system. Recall that von Economo reported insomnia (loss of sleep) in patients who had suffered damage to the preoptic basal forebrain area. This may now be seen as due to the loss of the basal forebrain GABA inhibitory influence upon the posterior hypothalamus. Without the basal forebrain inhibitory influence, the histaminergic arousal system remains active and prevents sleep. Szymusiak and McGinty (1986) showed that insomnia in basal forebrain-lesioned cats could be reversed with an injection of muscimol, a drug that mimics the effects of GABA, into the posterior hypothalamus. In addition to the basal forebrain projection to the hypothalamus, there is evidence that this population of inhibitory neurons also projects to the peribrachial nuclei of the brain stem reticular activating system and contributes to the basal forebrain induction of sleep.

There has always been an interest in exploring chemical factors that produce sleep. An easy-to-understand impetus for this is the simple observation that as one remains awake for a number of hours, a feeling of tiredness and an urge to sleep becomes stronger. It is as if a chemical factor builds up and the longer one stays awake, the more this chemical accumulates. When sleep occurs, the chemical is removed or metabolized and the urge to sleep is removed.

A classic approach to this area of interest has been to deprive animals of sleep and extract chemical substances from the brain, blood, cerebral spinal fluid, or urine and inject them into non-sleep-deprived animals. Control animals, of course, receive similar infusions from non-sleep-deprived donors. Positive findings were reported as early as 1909 by Ishimori in Japan and in 1913 by Piéron in France. Since then more advanced procedures have also yielded findings and in some cases the active agent has been characterized (Monnier et al. 1963; Pappenheimer et al. 1967; Schoenberger and Monnier 1977; Nagasaki et al. 1980).

Two major questions arise: the origin of the chemical factor and the site of action in the brain that causes the sleep. Krueger et al. (1985) discovered the complex chain of events that produces increased sleep during an illness produced by a bacterial infection. Invading bacteria stimulate phagocytic cells of the immune system to incorporate and digest the disease-causing bacteria. The skeletal residues of bacteria include circulating muramyl peptides that stimulate the immune system to synthesize a number of protein molecules, cytokines, that in turn stimulate a population of hypothalamic cells to produce the growth hormone releasing hormone (GHRH). Endocrinologists

have long known that GHRH produced by the hypothalamus travels by a blood-borne route to the anterior pituitary and causes the release of growth hormone from the pituitary gland. Another group of cells in the hypothalamus also produces GHRH, but these cells project axons to the nearby basal forebrain–preoptic area. The GHRH, now as a neurotransmitter, activates the GABAergic basal forebrain cells to inhibit the arousal systems of the posterior hypothalamus and brain stem reticular formation and thus produce sleep.

Robert McCarley and colleagues at Harvard University have explored an endogenous chemical that produces sleep in non-pathological, normal conditions. Adenosine is a purine product of the breakdown of adenosine triphosphate (ATP) during cellular metabolism. This occurs in all cells, including nerve cells. Extracellular fluids from two brain regions were sampled during sleep and waking in cats. Increased amounts of adenosine were present in both samples taken during the waking state compared with the sleep state (Porkka-Heiskanen et al. 1997). Since neural activity, and thus brain cell metabolism, is greater during waking than in sleep, the increased metabolite, adenosine, is not surprising. The two brain regions investigated were the basal forebrain, known to regulate sleep and arousal, and a nucleus of the thalamus that is not involved in regulating these states. Both groups of cells were more active in the waking state and both generated increased amounts of adenosine during waking. However, of interest and importance is the observation that the basal forebrain neurons, in contrast to the thalamic cells, possess adenosine receptors. One class of these receptors, A_1 adenoreceptors, opens potassium channels and this results in an efflux of this positive ion to produce a hyperpolarization of the cell. An increase of internal negativity is a neural inhibitory condition. The clear inference is that when the cholinergic cells of the basal forebrain are more active to produce arousal, increasing amounts of adenosine are generated that eventually feed back to act on the adenosine A_1 receptors of these same cells to decrease their activity and thus reduce arousal. McCarley's group (Thakkar et al. 1999) directly tested this position by applying different concentrations of an A_1 receptor agonist to the basal forebrain. They demonstrated a dose-dependent decrease in the activity of these cells. Thakkar et al. (2002) also reported that the hypocretin arousal-producing cells of the posterior hypothalamus also possess adenosine A_1 receptors that would serve to dampen arousal. Similarly, the cholinergic cells of the brain stem reticular activating system possess adenosine receptors that function in a negative feedback process to self-regulate arousal. An emerging view is that the final step in producing sleep is an inhibition of cells in regions of the brain that produce arousal. The source of inhibition may be other brain regions or may result from a self-regulating process inherent in the arousal system cells themselves.

The neural control of REM sleep

In 1953, a discovery by Eugene Aserinsky, a graduate student at the University of Chicago, and Nathaniel Kleitman, his mentor, triggered an immense interest in the scientific study of dream sleep – as well as the study of sleep in general. They reported that during episodes of dream sleep, transient rapid eye movements (REMs) were readily detected and could be documented on the same paper record as the EEG waves. In addition, they found that the EEG recorded during dream sleep closely resembled that of an awake, alert brain (Aserinsky and Kleitman 1953). These two measures (REMs and an awake-like EEG) were the first objective indicators of the occurrence of dream sleep. Kleitman's sleep laboratory soon showed that all the subjects studied had REM sleep. Even those who claimed they did not dream, when awakened during a REM episode reported having a dream experience. It should be pointed out that over the years since the Aserinsky and Kleitman findings, there have been reports of dream episodes when subjects were awakened from slow-wave sleep. Not all of these reports can be dismissed as recollections of dreams that occurred during a previous REM episode because some of these reports occurred prior to the first REM period.

As these findings on REM sleep were being generated, William Dement, another student in Kleitman's laboratory, discovered the presence of REM sleep in cats (Dement 1958). Very shortly after, Michel Jouvet in Lyon, France, as well as other workers over the years, reported that REM sleep episodes occurred in all mammalian species investigated and was seen also in other vertebrates, but in limited amounts (Jouvet et al. 1959; Jouvet and Valatx 1962; Ruckebusch 1962; Adey et al. 1963; Faure et al. 1963; Roldan et al. 1963; Hartmann et al. 1967; Shurley et al. 1969; Cicala et al. 1970; Schlehuber et al. 1974; Latash and Galina 1975; Allison et al. 1977; Siegel et al. 1996, 1999). REM sleep was shown to be a universal phenomenon in mammals and dream sleep in humans could no longer be relegated solely to the occult or to the psychoanalytic couch. REM sleep, and sleep in general, was now taken seriously as a legitimate subject for scientific investigation.

REM sleep has been differentiated from slow-wave sleep in both humans and animals on the basis of a number of physiological measures. The most obvious were the rapid eye movements themselves and the awake-like EEG brain recordings. In addition there is an irregular heart rate and increased blood pressure, respiratory rate, and pupil diameter. These autonomic changes indicate a heightened state of sympathetic activation. During REM episodes, males show penile erection and females exhibit comparable signs of sexual arousal. Non-autonomic components of REM sleep also are present. Muscle tone in striated-skeletal muscle is abolished. There is essentially a paralysis of the whole body – with the exception of extraocular muscles that control eye movements and, most importantly, muscles of the diaphragm that control respiration. Another component of REM sleep is the occur-

rence of spike-like transient waves recorded from electrodes in the pons, lateral geniculate nucleus of the thalamus, and the occipital (visual) cortex. These intermittent discharges are called PGO waves. Finally, electrodes placed into or close to the hippocampus show a very regular six per second EEG rhythm called theta waves.

The biological or psychological significance of these REM sleep components are in some cases clear, and in other cases obscure. For example, the low-voltage, fast-activity EEG recorded from the cortex indicates a cognitively active brain, which is appropriate for the dream state. The sympathetic activation suggests that dreams are periods of emotional arousal and the paralyzed skeletal musculature prevents the dream episode from being acted out. In contrast, the “meaning” of hippocampal theta and PGO spikes is not known.

From the mid 1950s, the neural control of REM sleep and its component parts have been intensively studied. Using the technique of surgical separation of the neuraxis at different levels of the brain stem, investigators have isolated the neural control of REM sleep to the pontine brain stem (Batini et al. 1959a, 1959b; Jouvet 1962; Siegel 1985). Additionally, finely placed lesions and focal brain stimulation within the pons and adjacent regions have revealed the cell groups responsible for a number of the components of REM sleep.

One of the most salient features of REM sleep is the awake-like EEG during the sleep state. As might be expected, the cholinergic peribrachial nuclei at the pontine–mesencephalic junction, in conjunction with a neighboring region in the pons, is now recognized as the source of the activated cortex during REM/dream sleep. Consistent with the observation that dream sleep is emotionally charged, brain-imaging studies indicate that the ventral arousal pathway, which engages the hypothalamus and other limbic system structures, subserves the cortical arousal during REM sleep (Maquet et al. 1996; Braun et al. 1997; Nofzinger et al. 1997).

Another prominent component of REM sleep is the profound paralysis of skeletal muscles. REM sleep paralysis has been shown to be due to a small region of the dorsal pons, the nucleus subcoeruleus. A lesion to this nucleus abolishes the REM sleep paralysis. A very dramatic observation is that during REM sleep, cats with such lesions became very active and agitated, as if they were acting out an emotionally charged dream episode (Sastre and Jouvet 1979; Hendricks et al. 1982).

The fact that there are multiple components to REM sleep suggests that multiple brain regions are involved in the control of this state. Studies suggest that the onset and offset of REM sleep are controlled by nuclei and connecting circuits within the pons and medulla. Two papers published in *Science* in 1975 (Hobson et al. 1975; McCarley and Hobson 1975) presented a model of reciprocal interaction between the neural activities of two populations of cells that result in the onset and offset of REM sleep episodes. With the empirical data collected at the time, this was an elegant attempt to explain, in neural terms, the cycling process between periods of slow-wave

sleep and REM sleep. Since the publication of these papers, McCarley, Hobson, and others have collected additional data and have refined the model (Siegel 1985; Hobson 1988; Steriade and McCarley 1990; Hobson et al. 1998; Xi et al. 1999; Chase and Morales 2000).

A current view is that the onset/offset of REM sleep is due to increased activity of cholinergic cells of the peribrachial nuclei of the mesopontine brain stem. Increased firing of these cells produces the cortical and limbic system activation seen during REM sleep. The offset of REM sleep and the descent into slow-wave sleep is due to increased activity of cells of the locus coeruleus and dorsal raphe nucleus, also in the pons, which release norepinephrine and serotonin, respectively. These aminergic neurotransmitters have an inhibitory effect on the cholinergic peribrachial neurons. The REM sleep episode is thereby terminated. Neural activities of the REM-on and REM-off nuclei are controlled by pontine negative feedback circuits that result in firing rates of these nuclei that are reciprocally related. REM-on and REM-off activities are also mediated by interneurons that utilize glutamate and GABA. Additional nuclei and neurotransmitters of the lower brain stem are recruited into the process and participate in the cortical arousal and muscle atonia that occur during REM sleep.

The function of sleep

An indication that a state of quiescence, if not sleep, is a very basic and important process is that all creatures, from single celled organisms to humans, exhibit activity cycles. There are periods of high activity levels interspersed with episodes of rest. In the common fruit fly, *Drosophila melanogaster*, episodes of rest may be considered as sleep, based on the following observations (Hendricks et al. 2000; Shaw et al. 2000). During periods of rest, a stronger sensory stimulus is required to elicit an orienting response. This is comparable to sleep, as we know it, during which a stronger stimulus is necessary to elicit a response. More to the point, if fruit flies are prevented from entering their resting state for a period of time and then permitted to do so, the insects will show an increased amount of time in the quiet state. This is comparable to the rebound of sleep time after a period of sleep deprivation has been imposed in mammals. This suggests that a homeostatic process regulates and programs a given amount of time for sleep in insects as well as in humans and other mammals. Moreover, periods of rest in *Drosophila* occur mainly during the dark phase of the 24-h day, which reveals a circadian rhythm comparable to the sleep–waking pattern seen in diurnal vertebrate species.

These observations, however, do not reveal the utility or function of sleep. The approach most widely used to explore this has been to deprive human and animal subjects of sleep and assess the effects. Since sleep clearly exists as two distinct states, workers have attempted to selectively deprive subjects of slow-wave sleep and of REM sleep. A complication is that REM sleep normally

only follows a period of slow-wave sleep, so deprivation of slow-wave sleep will also interfere with REM sleep. But selective REM-sleep deprivation is feasible – as is total sleep deprivation.

Evidence from the sleep literature suggests that sleep serves at least two functions. A series of studies by Allan Rechtschaffen and colleagues at the University of Chicago has shown the dire effects of sleep deprivation in rats. Within 2–3 weeks of total sleep deprivation all the rats died. Selective deprivation of REM sleep also proved lethal, with the difference that survival time was 1 or 2 weeks longer (Rechtschaffen et al. 1983, 1989; Bergmann et al. 1989; Kushida et al. 1989).

A number of changes occurred during sleep deprivation, but two have been identified as most important. Sleep-deprived rats increased food intake as much as 80–100% over their normal amount. However, they also showed a significant weight loss. The reason for the contradictory effects was a severe hypothermia that led to a great increase in metabolic rate in the effort to regulate body temperature toward a normal level. However, the proximal cause of death proved to be a bacterial infection that invaded the blood stream and spread throughout the body. A recent experiment detailed the underlying process. Everson and Toth (2000) found that the source of the bacteria was the gastrointestinal tract. Bacteria that are normally contained within the intestine proliferate during sleep deprivation, permeate the intestinal wall, and enter the internal environment. The mesenteric lymph nodes adjacent to the intestine normally protect against bacterial invasion from the intestine, but under sleep deprivation the immune system is compromised and ceases to defend against this invasion (Everson 1993). The bacteria proliferate, spread to other organs, and eventually enter the circulatory system to produce a systemic infection that is fatal. It should be noted that sleep deprivation, especially for long periods, acts as a non-specific stressor. Some workers question whether the sleep deprivation per se or the accompanying stress caused the dire effects described above.

These dramatic and extreme effects were produced in experimental animals. Humans normally do not experience such extreme conditions of sleep deprivation. Recent studies report that the immune system is compromised also by moderate sleep deprivation. After receiving vaccinations against influenza and hepatitis, subjects who experienced moderate sleep deprivation showed a reduced development of the antibodies that protect against these diseases (Spiegel et al. 2002; Lange et al. 2003).

There is a growing body of literature that suggests another function of sleep is the facilitation of memory consolidation. There is evidence that the process of memory storage of a learning experience is enhanced during a period of sleep that follows the learning. Experiments with humans and animals show that subjects who are trained on particular tasks and then permitted to sleep retain the learned information better than subjects who are prevented from sleeping after the learning.

Recognizing the possible confounding of the effects of sleep deprivation with the effects of stress, experiments have been designed to study the role of sleep in memory without using sleep deprivation. One form of this approach has been used in human and animal studies performed by Elizabeth Hennevin and colleagues at the University of Paris-South and Carlyle Smith at Trent University in Canada (Hennevin et al. 1995; Smith 1995, 1996). These workers capitalized on the observation that the learning curves of individual subjects do not show improved performance in a smooth incremental fashion, as the classical group learning curve is usually shown. For individuals, small daily improvements occur, and then, on a particular day, a large improvement in performance will occur. This pattern persists until performance reaches a plateau. Hennevin's and Smith's groups observed a marked increase in the amount of REM sleep during the sleep period just prior to a session in which there was a large improvement in performance. The clear inference is that during the increased amount of REM sleep time, a greater amount of memory processing had occurred – and the subsequent session showed the improved performance. When performance leveled off and, presumably, no further memory consolidation had occurred, the amount of REM sleep returned to the baseline levels that had been measured during sleep prior to the learning sessions.

Recent work by Stickgold et al. (2000a, 2000b), using human subjects, showed that improved performance did not occur after learning trials unless sleep was permitted within 30 h of the training. They further showed that memory consolidation is a two-step process. The amount of performance increase following a night's sleep was proportional to the amount of slow-wave sleep during the first 2 h of sleep and also proportional to the amount of REM sleep during the last 2 h of sleep. Their data support the contention that slow-wave sleep during the beginning hours of sleep and REM sleep toward the morning are both important for the consolidation process.

A great deal of effort is currently directed toward exploring whether certain types of learning and memory are selectively consolidated during REM sleep versus non-REM sleep (Smith 1996, 2001; Plihal and Born 1997, 1999; Gais et al. 2000; Stickgold et al. 2000a, 2000b; Ribeiro et al. 2002; Davis et al. 2003; Graves et al. 2003). Numerous theories have been proposed for the salutary effect of sleep on memory consolidation. These range from a form of practice or rehearsal during dream sleep (Fishbein and Gutwein 1977, 1981) to neuromolecular changes such as increased protein synthesis during sleep that strengthen recent memory traces (Ramm and Smith 1990; Nakanishi et al. 1997; Van Cauter and Spiegel 1999; Frank et al. 2001; McDermott et al. 2003). The role of sleep in memory is a heavily researched topic and is by no means settled. Numerous review and research papers have been written on this topic (Smith 1996, 2001; Buzsaki 1998; Graves et al. 2001; Maquet 2001; Siegel 2001; Stickgold et al. 2001; Pace-Schott and Hobson 2002).

This broad-ranging review on sleep and waking has presented historical material that has been basic to the current advances in research on this topic. The nuclei and neural circuits of the brain stem and other subcortical areas that control waking, slow-wave sleep, and REM sleep were described. Finally, functions of sleep related to the immune system and memory were discussed.

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