Feature Article

Sleep and Dreaming

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With its increasing emphasis upon functional questions, sleep research has entered a new and exciting third phase. Since sleep had never been objectively studied in any detail prior to the beginning of its first phase in about 1950, it was to be expected that much of the early work in the field would be descriptive. (For reviews of the early work, see Jouvet, 1972; Moruzzi, 1972.) Sleep proved a more complex behavior than such distinguished physiologists as Pavlov (1960) and Sherrington (1955) had imagined, and, even today, new discoveries continue to be made, especially in the clinical realm. In the second phase of sleep research, beginning about 1960, specific mechanistic theories began to be enunciated and tested. New cellular and molecular research techniques produced a spate of findings that have gained conceptual and empirical coherence (Steriade and Hobson, 1976; Hobson et al., 1986; Hobson, 1988). While incomplete, the mechanistic approach is still going strong, promising to inform—and be informed by—the third phase research on sleep function that has recently been initiated (see reviews, Hobson, 1988, 1989).

Chapters on sleep are most often placed at the end of modern treatises of neurobiology, indicating that sleep is regarded as an evolutionarily recent, emergent, and “higher” function of the brain. In its fully developed form in humans—a cycle of dreamless Non-Rapid Eye Movement (NREM) sleep followed by Rapid Eye Movement (REM) sleep accompanied by dreaming—sleep is clearly a complex function (see Fig. 1); yet, even in unicellular organisms or single cells, sleeplike behavior is present, organized differentially over time in sequential phases of rest and activity, responsiveness and unresponsiveness (Aschoff, 1965a; Moore-Ede et al., 1983). The circadian rhythm is the best known example of the temporal organization of physiological functions, but rhythms with shorter (infradian) and longer (ultradian) periods are now widely recognized. Thus it would seem that the rhythm of rest and activity (the primordia of sleeping and waking) is one of the most universal and basic features of life.

While rest states are seen in all organisms, sleep as we define and measure it in homeothermic mammals has many significant features not seen in lower animals. Thus, although the reptiles and birds have both EEG synchrony and diminished responsiveness (as in mammalian NREM sleep), they evince no REM phase despite having all the brain-stem structures used by mam-

mals to activate their brains periodically in sleep. The only exceptions are birds, who show brief REM episodes in the first few days after hatching. They lose this sleep state as they mature, thus paralleling the dramatic decline in sleep—and especially REM—in all young mammals (Roffwarg et al., 1966). Amphibia have none of the sleep features of mammals and, unless their temperature falls, they remain constantly alert even when immobile and relaxed for long periods of time.

I begin this essay by describing the most recent findings regarding sleep function, not only because they are exciting in their novelty, but because they strongly support some of our commonsense notions about the importance of sleep. Research to date has clearly demonstrated that sleep is essential, not only to health, but to life itself through its ability to regulate the flow of energy. I go on to suggest that the metabolic, thermoregulatory, and information-processing functions of the animal may be coordinated by the organized sequences of waking and sleeping states and that the brain's control of these sequences proceeds via an ebb and flow of aminergic and cholinergic effectors within the brain.

As suggested by Hess (1954), the aminergic system controls ergotropic (energy expending) functions, whereas the cholinergic system controls trophotropic (energy conserving) functions. Because the aminergic and cholinergic effectors modulate neuronal activity through processes occurring both at the membrane and within the cell, it seems likely that the robust differences in sensory information processing that distinguish waking from sleeping may be explained by the same mechanisms. Thus these modulatory systems appear to control input gating (i.e., determining whether signals reach the CNS), internal signal generation (i.e., establishing the source and intensity of spontaneous central stimuli), and how signals of either provenance are processed (i.e., determining whether they are stored in the brain and, if so, where and in what form). These 3 operations are subsumed under the concept of “information processing” in this paper.

Although no theory about sleep functions is universally accepted at present, and all theories remain subject to revision in the light of new data, specific models now seem indispensable for organizing and interpreting the myriad of findings (see, for example, Fig. 2). In any case, it is already clear that because sleep is a global organismic phenomenon, its study can integrate in an illuminating way many domains of behavioral and psychological science with neurobiology.

New insights in sleep function

Sleep and temperature regulation

Sleep onset normally occurs on the descending limb of the curve describing the circadian body temperature rhythm, and a further drop in body temperature occurs with the first episode of NREM

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Figure 1. Behavioral, electrographic, and neuronal activity changes associated with the sleep-wake cycle. *A*, Behaviorally, wake is characterized by frequent movements, logical thoughts, and accurate perceptions of external stimuli. NREM sleep is characterized by episodic posture shifts and limb movements, logical but nonprogressive thinking, and a sparseness of imagery. REM sleep is characterized by the near complete absence of body movements and dreams as complex and vivid as our wake-state thoughts, but with illogical thinking and bizarre perceptions. *B*, Electrographic changes correlate well with behavioral changes. Muscle tone, as measured by electromyogram (EMG), is highest in wake and absent in REM sleep, with NREM sleep intermediate, corresponding with the progressive reduction of movements seen from waking to REM sleep. Cortical EEG is as desynchronized in REM sleep as in wake, correlating with the complexity of thought and vividness of imagery observed in both states. During NREM sleep, high-amplitude delta (1–4 Hz) waves, which are correlated with decreased mean neuronal firing rates, appear in the EEG, as do spindle complexes. These observations correlate well with the low level of mental activity and lack of dream imagery reported in NREM sleep. Electro-oculographic (EOG) potentials are common to both REM sleep and wake, but are largely absent in NREM sleep. In wake, these EOG potentials represent eye movements tracking external stimuli, while in REM sleep they appear to be generated internally. Ponto-geniculo-occipital (PGO) waves are absent in NREM sleep and can be recorded in wake in association with a startle response. In contrast, clusters of PGO waves can be recorded in the brain stem, thalamus, cortex, and some subcortical structures during REM sleep. Since few environmental stimuli reach the brain in REM sleep, it is unlikely that these PGO waves represent a reflexive component of the startle response, but rather operate independently in REM sleep as a source of excitation to the forebrain. *C*, Neurons of the locus coeruleus (LC) and the dorsal raphe nucleus (DRN) the principal sources of norepinephrine (NE) and of serotonin (5HT) delivered to the forebrain, respectively, both exhibit their highest rates of tonic discharge in wake (W). During NREM sleep (N), LC and DRN firing rates are decreased to 50% of wake-state levels, but in REM sleep (R), the LC and DRN cease firing almost completely, removing the modulatory influences of NE and 5HT from forebrain processes. The ordinate axis represents the mean neuronal discharge rate per minute. Spike trains are recorded from a single cat DRN neuron. (Modified from Mamelak and Hobson, 1989).

sleep. Furthermore, 2 distinct thermal adaptations, shallow torpor (a temperature drop occurring daily in small mammals) and hibernation (a more profound and prolonged seasonal drop in body temperature) occur during NREM sleep (Heller et al., 1988). These facts combine to favor the view that sleep is part of a continuum of diverse energy conservation strategies used by mammals to cope with varying levels and sources of heat and light. Whatever benefits sleep may accrue for tomorrow, one clear function is to conserve calories for today.

In addition to a drop in body temperature, reduced responsiveness to changes in ambient temperature is also observed in NREM sleep; shivering in response to cold and sweating in response to heat are both diminished. Once NREM sleep is established and the temperature nadir is passed, REM sleep supervenes, during which thermoregulatory reflexes disappear altogether. In recent studies of the brain basis of these phenomena, Heller and coworkers at Stanford (1988) and Parmeggiani and colleagues in Bologna (1988) have shown that the respon-

Figure 2. Schematic representation of the REM sleep generation process. A distributed network involves cells at many brain levels (*left*). The network is represented as comprising 3 neuronal systems (*center*) that mediate REM sleep electrographic phenomena (*right*). Postulated inhibitory connections are shown as *solid circles*; postulated excitatory connections as *open circles*. In this diagram no distinction is made between neurotransmission and neuromodulatory functions of the depicted neurons. It should be noted that the actual synaptic signs of many of the aminergic and reticular pathways remain to be demonstrated, and, in many cases, the neuronal architecture is known to be far more complex than indicated here (e.g., the thalamus and cortex). Two additive effects of the marked reduction in firing rate by aminergic neurons at REM sleep onset are postulated: disinhibition (through removal of negative restraint) and facilitation (through positive feedback). The net result is strong tonic and phasic activation of reticular and sensorimotor neurons in REM sleep. REM sleep phenomena are postulated to be mediated as follows: EEG desynchronization results from a net tonic increase in reticular, thalamocortical, and cortical neuronal firing rates. PGO waves are the result of tonic disinhibition and phasic excitation of burst cells in the lateral pontomesencephalic tegmentum. Rapid eye movements are the consequence of phasic firing by reticular and vestibular cells; the latter (not shown) directly excite oculomotor neurons. Muscular atonia is the consequence of tonic postsynaptic inhibition of spinal anterior horn cells by the pontomedullary reticular formation. Muscle twitches occur when excitation by reticular and pyramidal tract motoneurons phasically overcomes the tonic inhibition of the anterior horn cells. Anatomical abbreviations: RN, raphe nuclei; LC, locus coeruleus; P, peribrachial region; FTG, gigantocellular tegmental field; FTC, central tegmental field; FTP, parvocellular tegmental field; FTM, magnocellular tegmental field; TC, thalamocortical; CT, cortical; PT cell, pyramidal cell; III, oculomotor; IV, trochlear; V, trigeminal motor nuclei; AHC, anterior horn cell. (Modified from Hobson et al., 1986).

siveness of temperature sensor neurons in the preoptic hypothalamus dips to a lower level in NREM sleep than in waking, and bottoms out in REM sleep. In sleep, the animal apparently substitutes behavioral control for its neuronal thermostat. It seems unlikely that an animal would develop such a high-cost maneuver in order to gain only a small and short-term caloric saving.

Daily variations in human body temperature of 1.5°C were observed in the first phase of sleep research and led to the discovery of the circadian rhythm (Aschoff, 1965b), which is now widely believed to be regulated by the suprachiasmatic

hypothalamus (Moore, 1979). The circadian rhythm of body temperature has been shown to be tightly coupled to the circadian rhythm of sleep and waking, and the degree to which these can be dissociated continues to be debated. In recent studies, Zulley and Campbell (1985) showed that subjects isolated from time cues were likely to enter long sleep episodes only at or near body temperature minima. Sleep was virtually impossible at other points on the body temperature curve. Naps could occur at other times, but sleep was not maintained. These studies questioned the previously reported phenomenon of "internal desynchronization" of the 2 rhythms by showing that the ob-

served desynchronization was in part an experimental artefact arising from injunctions not to nap, which led to the underreporting of sleep by subjects taking part in the original bunker experiments (Aschoff, 1965b). The dual oscillator theories resulting from these studies—one oscillator for body temperature and the other for sleep—have stimulated elaborate modeling efforts (Kronauer et al., 1982; Gander et al., 1984). An important problem to be solved is the neural basis of the usually strong coupling between the hypothalamic circadian oscillator and the pontine infradian sleep oscillator. Complementing earlier reports of surgical dissociation of the oscillators, Jouvet and colleagues (1988) have recently shown that the 2 oscillators can also be chemically uncoupled. However, the cellular and molecular basis of the circadian oscillator and the mechanism of its coupling to the other oscillators remains to be fathomed.

Sleep deprivation is fatal

Because mental lapses and fatigue are the well-known sequelae of even moderate sleep deprivation, common sense has long held that sleep is as essential to effective information processing as it is to energy homeostasis. But, because convincing experimental models of these phenomena have not been available, the underlying pathophysiology of the deficit states and the mediating variables of sleep's supposed benefits have not been elucidated. The discovery of sleep's periodic NREM and REM phases retarded progress in this area, by inducing scientists to make fruitless attempts to differentiate between a hypothetical energy-restoration function for NREM sleep and a cognitive or information-processing function for REM sleep.

Long-term sleep deprivation in rats has recently been shown to produce impaired thermoregulation, metabolic dyscontrol, and death. Studies by Rechtschaffen and coworkers (1989a, b) demonstrated this by using an ingenious experimental set-up. A vertical plexiglas cylinder is divided longitudinally into 2 chambers, each housing a rat with *ad lib* access to food and water (Bergmann et al., 1989a). The physiological activity of both rats is continuously monitored. One of them, the index rat, is sleep deprived and, as soon as it shows EEG slow waves presaging the onset of sleep, the circular cage floor moves, causing arousal. The physiological activity of the control rat has no influence on the motion of the floor. Index and control rats experience the same spatial dislocation. But the control rat can sleep whenever the cage floor is not moving. Increasing differences in the sleep debt of the 2 rats can be measured (Everson et al., 1989a). Using this device, animals can be selectively deprived of either REM sleep or both NREM and REM sleep (Gilliland et al., 1989; Kushida et al., 1989a). Qualitatively, the results are the same: when continued long enough, sleep deprivation is invariably fatal, and the premonitory syndrome invariably involves impaired thermal and metabolic control (Bergmann et al., 1989b). Thus REM sleep deprivation alone is capable of causing homeostatic failure.

After one week of total sleep deprivation, rats show a progressive weight loss, which occurs even in the face of increased food intake and hence cannot be due to loss of appetite (Bergmann et al., 1989b). Nor is weight loss simply an exercise effect, because the yoked control rats perform as much muscular work as the sleep-deprived index rats. And it is difficult to invoke stress as a mediator of weight loss unless stress is a specific consequence of sleep deprivation in the index rats. The progressive weight loss, which becomes more pronounced after 2 weeks, appears to be a syndrome of metabolic dyscontrol, which

causes more and more calories to be consumed in a vain attempt to restore lost energy homeostasis. While there are skin changes in the index rats (Kushida et al., 1989b), their immune function is not impaired (Benca et al., 1989). When deprivation is stopped, recovery is prompt and complete (Everson et al., 1989b). En route to each rat's ultimate demise at about 4 weeks of deprivation, body weight plummets, while food consumption soars, and body temperature becomes progressively more unstable.

These observations provide an excellent model for the investigation of what appears to be a progressive failure of energy-regulating mechanisms within the brain. Based upon what is now known of the cellular neurophysiology of sleep, and echoing Hess's ergotropic-trophotropic model, one attractive hypothesis is that sleep deprivation causes a progressive loss of aminergic synaptic efficacy, resulting from overdriving the sympathetic system on the one hand, and denying the respite from neurotransmitter release that normally occurs in sleep. According to this interpretation, aminergic discharge and/or transmitter release would increase as an initial response to sleep deprivation. However, as the sleep-deprived brain becomes more and more depleted of its sympathetic neurotransmitters, first cognitive, then thermal, and finally homeostatic caloric systems would fail. These and other hypotheses involving sleep-dependent neuroendocrine responses (such as growth hormone release) can be tested in the light of the new sleep deprivation paradigm.

Sleep and the immune system

It is well known that humans with infectious disease become sleepy, but the mechanism of this effect and its functional significance are not understood. Is this a consequence of increasing demands upon the sympathetic nervous system and upon energy metabolism, with more calories diverted to febrile and other defensive processes? Krueger and colleagues (1984, 1985a, b) have investigated the effects of sleep deprivation upon experimentally induced infection in rabbits, using *ad lib* sleeping, infected animals as a control, and a variety of specific immunological measures as well as clinical outcome as dependent variables. This work lies in the newly developing area of sleep and immune function interaction, particularly the capacity of interleukin-1 to promote sleep.

These experiments, still in progress, grew out of major work initiated by John Pappenheimer (1975), which identified the NREM sleep-promoting factor (S) in the spinal fluid of sleep-deprived goats and rabbits as a muramyl dipeptide (MDP). Muramyl peptides are not found in brain cells but are the building blocks of bacterial cell walls. They are powerfully pyrogenic and immunostimulatory, in addition to having somnogenic effects, which appear to be at least partially independent of their pyrogenicity (Krueger et al., 1985b). One particularly intriguing finding is the capacity of MDP to compete with serotonin at its binding sites on both CNS and immune system cells, suggesting a common mechanism linking MDP's somnogenic and immunostimulatory effects (Silverman et al., 1989).

Paralleling Pappenheimer's work was the investigation of numerous other molecules, including delta sleep-inducing peptide, DSIP, and the prostaglandins. These studies have raised further questions about the specificity and physiological significance of the several sleep factors, none of which has been shown to be present in effective amounts in sleep, as opposed to sleep-deprived, animals. At an extreme, all sleep factors could be regarded as artefactual and hence irrelevant to physiology. A more tolerant view regards each as playing a contributory role

Figure 3. The PGO system as a phasic source of cholinergic facilitation in REM sleep. *A*, Cholinergic input from the brain stem is widespread, as evidenced by the innervation of the rat forebrain by ascending cholinergic projections. (Reproduced with permission from Woolf and Butcher, 1986). *B*, PGO burst neurons recorded from the cat pontine brain stem (unit) precede PGO waves recorded in the lateral geniculate nucleus (LGB), and are considered the source of all PGO-like activity recorded in the forebrain in REM sleep. Ipsilateral PGO waves (LGBi) are larger than contralateral (LGBc) waves. (Adapted from Nelson et al., 1983.) *C*, PGO facilitatory input is viewed as a source of phasic EPSPs superimposed upon forebrain neuronal activity. When applied to already active neurons (*far left trace*), or neurons far below threshold (*far right trace*), PGO input has no influence. However, in neurons that are only slightly sub-threshold, cholinergic facilitation by PGO input may induce discharge in a neuron that would not otherwise fire (*middle trace*). *D*, The relationship between PGO wave-induced bifurcations and dream discontinuity is diagrammatically outlined by considering the development of a dream as a series of sequential input-output responses by the brain's neuronal networks. For a given input, a set of outputs ranging from improbable to likely exists, and the events that occur in a dream reflect the actual outputs that are generated (*dark arrows*). PGO input may facilitate the spontaneous discharge of enough neurons such that the resultant pattern of activity present when this facilitation stops is entirely unrelated to the range of possible or expected outputs prior to the PGO input. Cognitively, this sudden shift or bifurcation in activity could represent a dream discontinuity such as a scene shift. (Modified from Mamelak and Hobson, 1989).

in a multifactorial humoral system (Inoué and Schneider-Helmert, 1988).

Interleukin-1 is an immunostimulatory and somnogenic peptide which is endogenous, being produced by brain glial cells and macrophages. Both interleukin-1 and MDP enhance phagocytic tumoricidal and bacteriocidal activity; exposure of B-lymphocytes to muramyl peptides results in increased antibody release, while interleukin-1 increases the proliferative response of T-lymphocytes and enhances interleukin-2 production. Interleukin-1 alters sleep in a manner similar to muramyl peptides; time spent in NREM sleep, amplitude of the EEG slow waves, and duration of individual episodes of sleep are all increased by this compound (Krueger et al., 1985a). However, because time spent in REM sleep is markedly decreased by both compounds, their contribution to the physiology of normal sleep remains uncertain. In this regard, it should be noted that Benca and colleagues (1989) did not find specific defects in immune function, even in severely sleep-deprived rats: spleen cell counts, as well as *in vitro* proliferation in response to mitogens and plaque-formation response to antigens by explanted lymphocytes were all normal.

Sleep and cognitive functions

Work on the cognitive neuroscience of sleep is tantalizing, but most of its promise remains unfulfilled. Early results indicated that learning (i.e., conditioned avoidance) in rats is followed by increases in REM sleep and is impaired by deprivation of REM sleep (Bloch, 1973; Fishbein et al., 1974; Smith et al., 1974). Recent efforts to further detail these findings revealed that the increase in REM sleep following conditioned avoidance is quite prolonged (Smith et al., 1980; Smith and Lapp, 1986), and that REM sleep must occur at particular times after training in order for learning to occur (Smith and Butler, 1982).

In studies with humans, 2 interesting new findings using the deprivation technique substantiate the idea that sleep improves cognitive competence. Using subjective reports and an objective test, Mikulincer and colleagues (1989) showed that measures of attention, concentration, affect, and motivation declined with increasing sleep loss and that all these measures were powerfully sensitive to time of day. A trough in measures appeared between 0400 and 0800 hr, when sleep would normally be present, and a peak formed between 1600 and 2000 hr in the early evening. In a comparable study, Dinges (in press) awakened mathematics graduate students from recovery sleep following 48 hr of sleep deprivation and found that they could not perform—or even remember—the simplest calculation tasks. The problem with such studies is that their strongly correlative findings (brains do not work well when sleepy) do not establish the causal hypothesis (brains work well because of sleep).

Contrary to common sense and most sleep research findings, the provocative theory of Crick and Mitchison (1983) states that we have REM sleep (and dreams) in order to forget. At a deeper level, with its emphasis on ridding the brain of parasitic resonance, the theory fits well with early work that suggested that sleep-starved brains have a higher propensity for seizure than sleep-sated brains (see Elazar and Hobson, 1985). It addresses a long-standing problem in neuropsychology: how brains distinguish between trivial and important associations and memories (Hartley, 1801; Luria, 1968). A good theory of sleep would account for both aspects of our experience—the capacity to remember some things and to forget others. And it would do so

automatically, that is, without a supervisor, as Crick and Mitchison point out.

There are 2 ways, not yet clearly articulated in any theory, that such sorting could occur, and both take into account the internal resonance templates or schemata postulated by Llinas (1988). Procedural memories might be reinforced through the interaction of a fixed repertoire of motor commands (issued automatically by the brain stem during REM sleep) and synaptic hotspot residues of daily sensorimotor experience (stored, for example, in the cerebellum; Ito, 1976; McCormick and Thompson, 1984); declarative memories might be reinforced (by hot spots in the forebrain, for example) through interaction with fixed action programs of affective and vegetative behaviors programmed in the limbic system. Our dreams clearly reflect some such integrative process; they are constantly animated and we move through diverse settings, combining both recent and remote experience in an emotional climate often fraught with strong feelings of anxiety and fear. According to this view, the idiot savant would suffer not only from the effects of heightened synesthesia, but from a failure of cognitive networks to resonate with the affective systems of the brain (Luria, 1968).

The problem with all these attractive ideas is that they are difficult to test experimentally in living animals. Thus one of the most attractive aspects of the Crick-Mitchison theory is its heuristic resort to neural net behavior in computerized brain simulations. This idea is now being pursued further by cognitive neuroscientists interested in modeling differences in information processing during the waking and dreaming states and especially such dream features as discontinuity and incongruity (Mamelak and Hobson, 1989; and see Fig. 3).

Another option for the cognitive neuroscience of sleep is a more aggressive and imaginative use of experiments in nature, for example, the clinical study of patients with brain lesions. It has already been shown that patients with either lesions of the pontine tegmentum, which damages the REM sleep generator (Lavie et al., 1984), or lesions of the left parietal cortex, which disconnects the occipital and temporal cortices integrating visual data with narrative structures, do not dream (Greenberg and Farah, 1986). While brain-stem-lesion patients lose REM sleep entirely, cortical-lesion patients lose only dreaming. Are there differences in what two such different kinds of patients can learn (or at least not forget)?

Recent progress in the cellular neurophysiology of sleep

While debate continues on the precise architecture and dynamics of the NREM-REM sleep cycle control system, there is widespread agreement on the following points: (1) The critical neurons are localized in the brain stem, principally the pontine tegmentum (as Jouvet originally suggested in 1962); but, (2) the neurons are more widely distributed and more heterogeneous than originally thought. They are gathered in numerous nuclei and have a diverse chemical constitution and connectivity (see Figs. 2 and 3). This explains one of the great puzzles of sleep research: why REM sleep, whose control is clearly localized in the pons, can be neither completely abolished by local electrolytic lesions nor consistently evoked by local electrical stimulation. (3) Cholinergic neurons enhance some REM sleep events, and all or part of the REM sleep phase can be cholinergically stimulated; and (4) the aminergic systems have the opposite effect, with both noradrenergic and serotonergic neurons enhancing waking and suppressing REM sleep. Thus drugs which

augment noradrenergic and/or serotonergic activity tend to increase arousal but impede REM sleep, suggesting a cholinergic-aminergic, push-pull oscillatory control system of sleeping and waking (Karczmar et al., 1970). I will not define or argue here the merits of the reciprocal interaction model of this oscillator (McCarley & Hobson, 1975), since they have been extensively debated in a recent peer commentary format (Hobson et al., 1986).

Waking and sleep onset

The seminal conception of a midbrain reticular activating system (Moruzzi and Magoun, 1949) has been thoroughly elaborated and vindicated by the work of Steriade and colleagues (1982). Their studies revealed that direct projections of mesencephalic neurons excite the intrinsic relay neurons of the thalamus, depolarizing them and eliminating the IPSP-burst sequences that contribute to the EEG spindling pattern characteristic of sleep. The neurons of the thalamic reticular complex are simultaneously inhibited, preventing their contribution to the IPSP-burst sequences. Steriade has shown that, in mediating the fast-wave desynchronized EEG patterns characteristic of both waking and REM sleep, the reticular mechanisms are essentially the same at the cellular level.

The EEG spindles characteristic of slow-wave synchronized sleep are produced by shifts in thalamic and cortical activity patterns, creating what Steriade and Llinas (1988) term "the oscillatory mode." Two mechanisms contribute to this shift. In the first, a change in the degree of depolarization/hyperpolarization impinging upon the thalamocortical neurons alters the intrinsic membrane properties (including activation of a low-threshold Ca^{2+} -dependent spike, the persistent Na^+ current and a high-threshold Ca^{2+} conductance related to dendritic spikes, and several K^+ conductances) to convert the waking alpha into the sleep spindle EEG rhythm. In the second mechanism, the inputs from the reticular thalamic nucleus and local circuit neurons intrinsic to the thalamus (which are GABAergic and inhibitory) are gated by extrinsic signals arising in the brain stem, all of which decrease at sleep onset. These signals include: (a) cholinergic excitation from pedunculopontine and dorsolateral tegmental nucleus neurons, (b) midbrain reticular excitation (transmitter unknown), and (c) aminergic modulation from the locus coeruleus and dorsal raphe nucleus.

How then can we account for the phenomenological and physiological differences between the 2 fast-EEG-wave states, waking and REM sleep? Two important findings followed the discoveries of chemically differentiated neurons within the brain stem core. First, the outputs of the 2 major modulatory systems of the upper brain stem, the noradrenergic nucleus locus coeruleus (Chu and Bloom, 1973, 1974; Hobson et al., 1975; Aghajanian and van der Maalen, 1986) and the serotonergic dorsal raphe nucleus (McGinty and Harper, 1976; Trulsson and Jacobs, 1979), were found to be much lower during REM sleep than during waking. According to Aston-Jones and Bloom (1981a, b), the phasic activity of these modulatory systems during arousal provides the cortex with a signal-sharpening capability that could enhance early stages of stimulus detection and discrimination (see review, Foote et al., 1983). Later stages of signal processing (i.e., learning and memory) may be related to the steady (tonic) activity of these same modulatory systems during the waking state and help to account for the strong state-dependent nature of learning and memory (Flicker et al., 1981; Hobson and Schmajuk, 1988). Thus the near-complete suppression of output

of the locus coeruleus and the dorsal raphe nucleus to the cortex in REM sleep could account for the twin paradoxes of inattention to and amnesia for our dreams, despite fast-wave EEG activity and vivid consciousness during that state (Hobson, 1988).

Second, the cholinergic neurons of the pedunculopontine nucleus were found to be under inhibitory restraint during waking by the aminergic neuromodulators, so that they fire only in response to strong and/or novel stimuli. Thus informationally critical stimuli co-activate both cholinergic and aminergic neurons in waking, and the result is the co-release of acetylcholine, serotonin, and norepinephrine in the forebrain. At NREM sleep onset, the cholinergic neurons become inactive. As NREM sleep proceeds, cholinergic neurons begin to develop a spontaneous burst pattern, possibly owing to disinhibition as the aminergic influences decline, providing the thalamus with strong pulses of cholinergic modulation and causing the onset of REM sleep (see Fig. 3). This occurs in the absence of external stimulation and with little or no co-activation of the aminergic neurons. Thus, in the 2 fast EEG-wave states, waking and REM sleep, the aminergic and cholinergic systems show out-of-phase reciprocal activity.

Missing from this appealing picture is specific information as to how the reticulothalamic or aminergic neuronal systems are gated, as they must be, by the circadian clock in the hypothalamus. The serotonergic neurons of the pons are known to project heavily into the suprachiasmatic nucleus, but the signal from the hypothalamus to the brain-stem oscillator is yet to be identified. In view of the exquisite sensitivity of aminergic neurons to peptide hormones and the abundance of peptides produced by the hypothalamus, a chemical message is the likely mediator of the phase-locking of circadian (rest-activity) and ultradian (NREM-REM sleep) rhythms.

Cholinergic REM sleep mediation

Confirming the early studies of Jouvet (1962) and Hernandez-Peón et al. (1963), numerous investigations have found prompt and sustained increases in REM sleep signs when cholinergic agonist drugs are microinjected into the pontine brain stem of cats (Hobson and Steriade, 1986). The behavioral syndrome produced by this treatment is indistinguishable from the physiological state of REM sleep, except that it is precipitated directly from waking with no intervening NREM sleep. The cats can be aroused but revert to sleep immediately when stimulation abates. This drug-induced state has all the physiological signs of REM sleep [such as fast-wave EEG, EMG atonia, REM, and pontogeniculo-occipital (PGO) waves], suggesting that it is a valid experimental model. Humans who are administered cholinergic agonists by intravenous injection during the first NREM cycle also show potentiation of REM sleep; this is associated, as usual, with dreaming (Sitaram et al., 1976).

Mixed nicotinic and muscarinic agonists (e.g., carbachol), pure muscarinic agonists (e.g., bethanechol; Hobson et al., 1983), and dioxylane (Vivaldi et al., 1979) are equally effective potentiators of REM sleep. Recent results suggest that activation of the M1 acetylcholine receptor suffices to trigger REM sleep behavior. The inference that acetylcholine induces REM sleep is suggested by Baghdoyan's (1984a) finding that neostigmine, an acetylcholinesterase inhibitor, which prevents the breakdown of endogenously released acetylcholine, also potentiates sleep after some delay. These effects are dose-dependent and are competitively inhibited by the acetylcholine antagonist atropine.

REM sleep induction is obtained only by injection of cholin-

ergic agonists into the pons; midbrain and medullary injections produce instead intense arousal with incessant turning and barrel-rolling behavior, respectively (Baghdoyan et al., 1984b). Within the pons, the response pattern differs according to the site of injection, with maximal effects obtained from a region anterodorsal to the giant cell field and bounded by the dorsal raphe and the locus coeruleus (Baghdoyan et al., 1987).

In the peribrachial pons, where both aminergic and cholinergic neurons are intermingled, carbachol injection produces continuous PGO waves by activating the cholinergic PGO burst cells of the region (Vivaldi et al., 1979; Nelson et al., 1983). But agonist induction of these drug-induced waves is state-independent, and REM sleep is not potentiated. By injection of carbachol into the sub- and peri-locus coeruleus regions of the pontine reticular formation, where tonic, neuronal activity can be recorded during REM sleep (Saito et al., 1977), atonia may be generated, while waking persists, suggesting a possible animal model of human cataplexy (Quattrochi et al., 1989).

Cholinergic cells of the PGO wave generator region of the peribrachial pons are known to project to both the lateral geniculate nucleus and the perigeniculate sectors of the thalamic reticular nucleus (Paré et al., 1988), where they are probably responsible for the phasic excitation of neurons in REM sleep (Hu et al., 1989a, b, c; Webster and Jones, 1988; Steriade et al., 1989). This supposition is supported by the finding that the PGO waves of the LGN are blocked by nicotinic antagonists (Hu et al., 1988). Singer's recent work (1989) suggests the functional significance of these internally generated signals. He proposed that the resulting resonance contributes to the use-dependent plasticity of visual cortical networks. Besides providing evidence that REM sleep signs are cholinergically mediated, these recent pharmacological results provide neurobiologists with a powerful experimental tool, since a REM-sleeplike state can be produced at will. Thus Morales and colleagues (1987) have shown that the atonia produced by carbachol injection produces the same electrophysiological changes in lumbar motoneurons as does REM sleep: a decrease in input resistance and membrane time constant, and a reduction of excitability associated with discrete IPSPs (Morales and Chase, 1981). These findings facilitate the exploration of other neurotransmitters involved in the motoneuronal inhibition during REM sleep, mediated at least in part by glycine (Soja et al., 1987).

Another important advance is the intracellular recording of pontine reticular neurons in a slice preparation (Greene et al., 1986). Neuronal networks can be activated cholinergically, producing the same electrophysiological changes as those found in REM sleep of intact animals (Ito and McCarley, 1984). A low threshold calcium spike has been identified as the mediator of firing pattern alterations in brain-stem slice preparations (Greene et al., 1986).

The activation process within the pons itself has also invited study, using carbachol as an inducer of REM sleep. Using the moveable microwire technique, Shiromani and McGinty (1986) showed that many neurons normally activated in REM sleep either were not activated or were inactivated by the drug. Yamamoto and colleagues (1988a, b) confirmed this surprising finding and found that the proportion of neurons showing REM-sleeplike behavior was greatest at the most sensitive injection sites.

To achieve greater anatomical precision in localizing the carbachol injection site, Quattrochi and coworkers (1989) have conjugated the agonist to fluorescent microspheres, thereby re-

ducing the rate of diffusion tenfold and allowing all neurons projecting to the injection site to be identified by retrograde labeling. Surprisingly, the behavioral effects are no less potent despite the reduced diffusion rate of the agonist and are maximized by injection into the same anterodorsal site described by Baghdoyan and colleagues (1987). That site receives input from all the major nuclei implicated in control of the sleep cycle: the pontine gigantocellular tegmental field (transmitter unknown), the dorsal raphe nuclei (serotonergic), the locus coeruleus (noradrenergic), and the dorsolateral tegmental and pedunculo-pontine nuclei (cholinergic). Thus the sensitive zone appears to be a point of convergence of the neurons postulated to interact reciprocally in order to generate the NREM-REM sleep cycle. Whether this is also a focal point of reciprocal projection back to those input sites can now be determined.

Clinical neurobiology of sleep disorders

Although the description of normal sleep is relatively advanced, discoveries of new sleep disorders continue to be made. As these and classical disorders of sleep are investigated, the frontiers of behavioral neurology widen and its foundation deepens.

REM sleep behavior disorders

One widely accepted concept holds that motor pattern generators are activated in REM sleep, which humans experience as dreamed movement. But since these motor patterns are quelled at the level of the spinal cord, we do not actually move. In other words, dreams are, in part, our conscious awareness and rationalization of automatic motor patterns that are activated in REM sleep—a variation of the concept of "fictive" behavior (Grillner, 1981). That humans, as well as cats, encode brain-stem-generated eye movement directional signals in the PGO waves of REM sleep has now been established (McCarley et al., 1983).

Until recently, it was assumed that somnambulistic episodes could arise only during NREM sleep, as originally demonstrated by Jacobson and colleagues (1965). This is because the active inhibition of spinal motoneurons (Pompeiano, 1967) and postural tonus (Jouvet and Michel, 1959) makes movement impossible in REM sleep, despite the activation of motor pattern generators in the brain stem. Indeed, normal animals evince only small twitches of facial and distal axial muscles in addition to eye movements.

Thus it was difficult at first to accept the claims of some late middle-aged males—confirmed by their spouses—that they occasionally acted out their dreams with comic but potentially harmful consequences. For example, one man hit his wife while dreaming of executing a sharp left turn in his car. Another, who was replaying a college football game in his dream, ran across the bedroom to tackle his chest of drawers, sustaining a severe laceration. Observed in the sleep laboratory, a wide range of motor behaviors—some fragmentary, some elaborate—do indeed occur in association with REM sleep in such patients (Schenck et al., 1986). A variety of neuropathologies, all affecting the pontine tegmentum, may underlie this abnormal motor disinhibition during REM sleep.

The major and paradoxical dissociations of motility and sleep state that were observed following lesions of the anterodorsal pons illuminate the probable pathophysiology of this REM sleep behavior disorder (Jouvet and Delorme, 1965; Henley and Morrison, 1974). Sequences of automatic movements, which suggested to Jouvet the rehearsal of elemental motor behaviors,

were seen in cats in conjunction with all the other EEG signs of REM sleep. This was especially true when the lesions disconnected the upper pons from the lower brain stem (Henley and Morrison, 1974). Such lesions are thought to have interrupted the pathway of the peri-locus coeruleus neurons (Sakai, 1985), which project to and excite the medullary inhibitory reticular formation cells (Netick et al., 1977), which in turn inhibit the spinal motoneurons.

Sleep in depression

It has long been recognized that the first episode of REM sleep occurs earlier, lasts longer, and is more intense in patients with major vegetative depression than in normal persons. This potentiation of REM sleep, which occurs together with a suppression of stage 4 NREM sleep, is likely to be an expression of the cholinergic hypersensitivity and the aminergic desensitization that contribute to the general pathophysiology of depression. When depression is relieved by tricyclic drugs, the sleep effects are also reversed, probably because blocking the re-uptake of norepinephrine and/or serotonin potentiates the enfeebled aminergic system. The drugs also have anticholinergic effects, which could contribute to weakening the excitability of the REM sleep generator network.

Recent work by Berger and colleagues (1985) has reinforced this basic story, while adding much interesting detail. First, it was found that the cholinergic agonist RS 87 aggravated both depression and the REM sleep abnormality. Second, subjects aroused from REM sleep naps were found to be more depressed than either before or after NREM sleep naps. Taken together with Vogel and Traub's (1968) report of the temporary relief of depression by REM sleep deprivation, these findings point to maladaptive overdriving of the cholinergic system as an important force in depression.

Genetic basis of narcolepsy

Narcolepsy has been known to be familial since its initial description by Gelineau in 1880. However, no clear genetic pattern emerges from pedigree studies, even when the diagnosis includes cataplexy and is not based only upon excessive daytime sleepiness. Patients with narcolepsy are much more likely (>99%) than unaffected individuals (30%) to carry a particular type of HLA DR2 antigen (Honda and Juji, 1988). But since being a carrier of the antigen does not predict the disease and many monozygotic twin pairs are of discordant narcoleptic phenotype, this trait must be considered predisposing rather than pathogenic. As to the underlying genetics of the DR2 antigen (which is found on the surface of many immune cells, including lymphocytes and macrophages), there are 16 alleles which are expressed codominantly, with each phenotype determined by the genes on both chromosomes 6. The studies to date have not clarified whether narcolepsy susceptibility is actually determined by an allele of the DRB gene or by a closely linked gene (Geisler and Albert, 1988). Among the many candidates for precipitation of the disease in susceptible subjects are viral and bacterial infections (Billiard et al., 1988), making the model of the disease analogous to juvenile diabetes and multiple sclerosis.

The pathophysiology of sleep apnea

The reduced activity of reticular formation neurons that characterizes NREM sleep is seen in respiratory neurons as well (Lydic and Orem, 1979). Thus it is normal for respiratory rates to fall at sleep onset, but in some individuals, predominantly

males, central respiratory drive falls to such low levels that breathing ceases altogether (i.e., they enter a state of apnea; Guilleminault and Dement, 1978). In REM sleep, when the reticular formation neurons are reactivated, their chaotic firing patterns may also contribute to centrally mediated apneas. As with the temperature control system of the hypothalamus (Heller et al., 1988; Parmeggiani, 1988), sensitivity to reflex adjustment declines dramatically in REM sleep. The hypoxia and hypercapnia that ensue upon cessation of breathing find the respiratory system less responsive (Phillipson, 1978). Some respiratory neurons cease firing altogether in REM sleep (Lydic and Orem, 1979). This is perhaps the most glaring and clinically significant illustration of the extreme state-dependence of the response to perturbation of all physiological systems. If this arrest of the central respiratory oscillator (so common as to be considered normal when it occurs less than 25 times per night!) is coupled with peripheral constriction of the airway, the results can be not only sleep-disruptive, but fatal. It is apparent that the functional benefits of sleep were not acquired without risk.

Conclusion

Modern sleep research has evolved from an early, descriptive phase through an increasingly detailed and precise analysis of the cellular and molecular mechanisms that regulate the NREM-REM sleep cycle. One unified theoretical model links aminergic neuronal functions to energy-expending states in which external data can be processed (waking), and postulates reciprocal interaction with cholinergic neuronal functions, which favors energy-conserving states in which internal data can be processed (REM sleep and dreaming). Attention is now being focused upon functional questions arising from studies of animals subjected to experimental deprivation in the laboratory and from experiments in nature involving human sleep disorders. Evidence from all these sources converges to suggest that sleep is a complex neurobiological and behavioral strategy for simultaneously promoting energy regulation and automatic information processing by the brain.

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