Chapter 31

Local and Use-Dependent Aspects of Sleep

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Chapter Highlights

- Variations in localized sleep intensity, as determined by electroencephalogram (EEG) slow wave power, are dependent upon prior awake activity.
- Unilateral application of sleep-promoting substances to the surface of the cortex enhances sleep intensity ipsilaterally, while inhibition of those substances decreases EEG slow wave power. Further, unilateral sleep states occur in marine mammals and some birds.
- Individual cortical columns oscillate between wake-like and sleep-like states with the percentage of columns in the wake-like state being high during whole animal waking and conversely with a high percentage of columns being in a sleep-like state during whole animal sleep states.
- Performance errors during a specific learned task dependent upon single cortical column activity are experimentally correlated with sleep- and wake-like states of the individual column.
- Co-cultures of dispersed neurons and glia manifest sleep- and wake-like states, as determined by neuron burstiness, synchrony of electrical activity, slow wave (0.25 to 3.5 Hz) power, gene expression patterns, sleep homeostasis, and spontaneously reversibility. Further, such cultures enter a deeper sleep-like state if treated with sleep regulatory substances and display more time in the wake-like state if excitatory amino acids or peptides are applied.
- Collectively these data indicate that small neuronal/glial networks are the minimum component of brains capable of sleep-like states and that the brain can simultaneously express sleep and wake states. This hypothesis provides fuller understanding to previously unexplained sleep anomalies such as sleepwalking, sleep inertia, poor performance during prolonged waking, insomnia, and other disassociated states.

INTRODUCTION

History

The simultaneous occurrence of sleep and wake states, such as that occurring during sleepwalking, has been evident to lay individuals for eons. Thus sleepwalkers appear to be asleep because they can be awakened and yet sometimes they can walk and navigate around objects as if awake. More recently the characterization of sleep inertia indicates that, upon awakening, it takes considerable time for cognitive performance to maximize, suggesting that parts of the brain are remaining in a sleep-like state. Conversely, with prolonged wakefulness, cognitive and behavioral performances deteriorate, suggesting that some of the small networks involved in carrying out the task are falling into sleep-like states.[1] Neurologists have also long recognized that unusual clinical observations (e.g., rapid eye movement [REM] sleep) in a patient with a behavior disorder, may be explained by state dissociations.[2] Thus sleepwalking, sleep inertia, deteriorating performance with prolonged waking, and disassociated states represent anomalies to the paradigm viewing sleep as an all-or-nothing, whole-brain phenomenon.

Retrospective reinterpretation of experimental evidence reinforces the concept that parts of the brain can be asleep while other parts are awake. For example, as early as 1949 waxing and waning of slow potentials, which we now know are associated with sleep states, were observed in isolated cortical islands lacking thalamic input yet retaining their blood flow.[3] After mid-pontine transection of the brain, the forebrain seems to oscillate between wake-like states and high-amplitude electroencephalogram (EEG) slow wave sleep (hereafter called non–rapid eye movement sleep, or NREM sleep) while posterior to the transection waxing and waning of REM sleep occur.[4] Slow stimulation of many areas of the cortex induces transient synchronization of the EEG that outlasts the period of stimulation. Indeed, Jouvet posited that if one used slow waves to define sleep, then the "entire encephalon has hypogenic properties."[5] Although Jouvet rejected this hypothesis, it likely is the initial recognition that sleep may be fundamentally a local process.

Dolphin unilateral NREM sleep determined using EEG measurements is a direct demonstration that sleep and wake states occur simultaneously within a brain.[6] Dolphins do not exhibit NREM sleep in both cerebral hemispheres simultaneously, and they also lack REM sleep altogether. Further, unihemispheric sleep deprivation leads to NREM sleep rebound in the ipsilateral cortex but not in the non–sleep-deprived

cortex.[7] This work has been extended to other marine mammals and to birds.[8]

There is substantial evidence that specific subcortical areas are involved in sleep regulation. However, it remains to be demonstrated that any of them are required for sleep expression. Thus, despite millions of poststroke clinical cases occurring in numerous parts of the brain and many experimental brain lesions to sleep regulatory areas, not a single postlesion human/animal has failed to sleep, albeit not always normally. For example, if rabbits are given large anterior hypothalamic lesions (a sleep regulatory area), duration of NREM sleep and REM sleep is greatly reduced. However, in the immediate postlesion period they remain responsive to sleep-inducing substances. Further, after a week or more of recovery, duration of spontaneous sleep returns toward prelesion values.[9] This experiment confirms the earlier work of von Economo,[10] confirmed by many others, showing that the anterior hypothalamus is involved in the active regulation of sleep. However, it also suggests, as did the stimulation data reviewed by Jouvet,[5] that multiple sites are capable of initiating sleep.

The work cited thus far led to the hypothesis that "sleep is basically use-dependent instead of simply wake-dependent; it explains why certain structures seem to be important for sleep regulation while their lesions will not elicit permanent insomnia. It suggests that sleep can be initiated at the local neuronal group level."[11] Within the past 28 years, this theory has been extended and clarified, and much experimental data have been generated in support of it. The remainder of this chapter summarizes those advances.

Definitions

There are several mental, behavioral, physiologic, and biochemical measures that correlate with sleep. Because there is no single measurement that is always indicative of when sleep is occurring, experimentally and clinically, two or more measures are usually used to characterize sleep (Box 31.1). Some of these characteristics are whole-brain or body properties, and whether those are useful to use as criteria for the identification of local sleep is debatable. Thus, for example, reduced locomotor activity is often used as a surrogate measure of sleep in fruit fly sleep studies. However, mammals severely infected with influenza virus are often motionless yet, as judged by their EEG, are awake. Similarly, sleepwalkers can walk yet simultaneously appear to be asleep as judged by mentation upon awakening. Regardless, many defining characteristics of sleep (red type in Box 31.1) occur locally in parts of the brain and even in vitro. For example, the EEG power in the rat visual cortex is higher during daylight hours followed by lower power at night. In contrast, the somatosensory cortex, which receives input from facial whiskers that rats use to navigate during the night, has higher EEG slow wave power during the night compared to the day.[12] Such results link a characteristic sleep EEG, the high slow wave amplitude, to local use dependency.

BOX 31.1 DEFINITIONAL CHARACTERISTICS OF SLEEP

- Reduced responsiveness to afferent input
- Reduced locomotor activity
- Distinct sleep postures
- Mentation quality
- Circadian rhythm linked
- Characteristic developmental patterns
- Spontaneously reversible
- Characteristic electroencephalogram wave forms
- Homeostatic regulation
- Characteristic neuronal firing patterns (e.g., burst/pause firing)
- Characteristic gene expression patterns
- Induced by sleep regulatory substances or suppressed by wake neuromodulators

The defining biologic characteristics of sleep are discussed in multiple chapters in this book. For whole animal sleep, characteristics include all those listed in this box. The list does not include all defining characteristics of sleep (e.g., changes in respiratory and cardiac frequency) and some that are specific to REM sleep vs. NREM sleep (e.g., variable respiratory and heart rates, compromised thermoregulation). The characteristics demonstrated thus far for local sleep in vivo are those in red. If a characteristic has also been demonstrated in vitro, it is underlined in addition. References for those in red are provided throughout this chapter.

LOCAL SLEEP PHENOTYPES

Local Electroencephalogram Slow Wave Power Is Dependent upon Waking Activity

The EEG slow wave power is often used as a measure of sleep intensity, for example, NREM delta wave sleep (old stage 4). Sleep intensity is identified by the occurrence of high-voltage slow waves and requires a more intense stimulus to awaken the subject than do stages 1, 2, or REM sleep. Localized EEG slow waves can be measured in multiple species, including humans, cats, rats, mice, chickens, and pigeons. If a localized area is disproportionately stimulated during waking, EEG delta power in that area is enhanced during subsequent NREM sleep.[12-18] Indeed, the first experimental test of the idea that sleep is a local use-dependent phenomenon used a hand vibrator to stimulate the contralateral somatosensory cortex for prolonged periods. In subsequent NREM sleep, EEG slow wave power was greater on the side that received enhanced afferent input.[19] As indicated, that finding has been replicated many times in multiple species. An eloquent demonstration that localized EEG slow wave power is quantitatively dependent upon afferent input was the demonstration that EEG slow wave power during NREM sleep was reduced in the somatosensory cortex if the subject's arm was immobilized during a 10-hour waking before sleep onset.[20] Such findings suggest that sleep intensity is dependent upon waking activity and is localized to the areas activated or inhibited.

Many additional human studies used transcranial magnetic stimulation to enhance local brain activity during waking and were followed by measurement of subsequent EEG slow wave power during sleep. These studies reached a similar conclusion: localized sleep intensity is dependent upon prior waking activity.[21,22] Further, functional magnetic resonance and positron emission tomography techniques have been used to similar ends. Thus such studies indicate that changes in localized cerebral blood flow or metabolism alter subsequent localized sleep.[23,24] Mechanistically, multiple sleep regulatory substances produced in the brain are vasodilators (Figure 31.1).

Experimental Manipulation of Unilateral Slow Wave Power and Sleep in Cortical Columns

To emphasize the sleep-linked roles of use-dependent molecules and their local origins, how they affect either sleep or sleep biomarkers at various levels of tissue organization is now

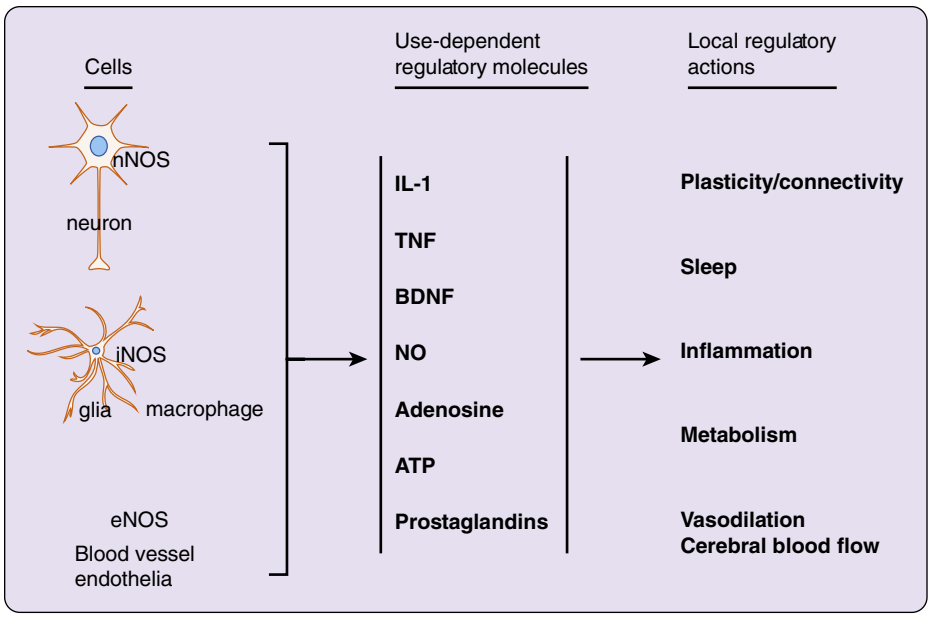

Figure 31.1 Brain cell types produce multiple sleep regulatory molecules in response to local cell use. These molecules initiate local events (*right*) that can emerge at higher levels of organization to alter multiple behaviors including sleep. ATP, Adenosine triphosphate; BDNF, brain-derived neurotrophic factor; eNOS, endothelial NOS; IL-1βb, interleukin-1β; iNOS, inducible NOS; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; TNF-α, tumor necrosis factor α.

presented. At the whole animal level, exogenously administered interleukin-1β (IL-1), tumor necrosis factor-α (TNF-α), growth hormone–releasing hormone, and brain-derived neurotrophic factor (BDNF) enhance sleep if given intracerebroventricularly or if injected into hypothalamic sleep regulatory areas, and all are well-characterized sleep regulatory molecules.[21,25] Unilateral localized injections of these substances onto the surface of the cortex enhances EEG slow wave power ipsilaterally, suggesting a deeper state of sleep at the injected side.[26-29] Conversely, inhibition of these substances reduces unilateral EEG slow wave power.[28,30,31] Cortical application of these substances also affects the cortical expression of each other.[32] Collectively, these experiments suggest, as evidenced by amplitudes of EEG slow waves, that locally acting sleep regulatory substances influence cortical sleep states unilaterally.

Within visual cortical receptive fields, the patterns of neurons becoming silent in monkeys performing a visual task as they fall asleep provide convincing evidence of local sleep and that it is regulated in a precise manner. Thus, as the behaving monkeys are falling asleep, some of the neurons stop firing; those neurons in the outer edges of the receptive field being engaged by the task are the first to stop firing. As sleep progresses into deeper stages and animals stop performing the visual task, neurons near the center of the engaged receptive field stop firing as well. Pigarev and colleagues concluded that this pattern of localized asynchronous development of sleep indicated that sleep is initiated as a localized process.[33]

Smaller local cortical networks, such as individual cortical columns, oscillate between wake-like and sleep-like states, as determined by their amplitudes of evoked response potentials (ERPs). When the subject is awake, ERPs are smaller in amplitude compared to ERPs occurring during sleep.[34-36] During waking periods, most of the cortical columns are in a wake-like state. In contrast, during whole animal sleep, most of the columns are in the sleep-like state. Individual columns also exhibit sleep homeostasis. Thus the longer an individual column is in the wake-like state, the higher the probability it will enter a sleep-like state. Further, individual cortical column state affects behavior. Thus Rector and colleagues[23] trained rats to lick a sweet solution in response to a facial whisker stimulation. If the somatosensory cortical column that received the whisker afferent input was in the wake-like state, the rat did not make performance mistakes. In contrast, if the column was in the sleep-like state, errors of commission and omission were made. Such results indicate that small local circuits in vivo oscillate between sleep and wake states. Local application of TNF to cortical columns induces higher ERP amplitudes, suggesting that sleep regulatory substances act at the local level to initiate sleep.[37] Further, because TNF and other sleep regulatory substances (Figure 31.1) are cell activity–dependent and prolonged wakefulness is associated with longer cell activation, the results also have implications for the poor performance outcomes in sleep-deprived subjects.[1] That in vivo cortical expression of IL-1, TNF, and BDNF upregulate with enhanced afferent input[38,39] and induce local sleep-like states suggests the local states and these molecules are driving the local enhancements of EEG slow wave power associated with enhanced localized activity during prior waking, as described previously.

Sleep In Vitro

As outlined previously, the definition of sleep as a whole organism behavior is insufficient to account for several network, cellular, and molecular aspects. To determine the minimal network capable of sleep, multiple other approaches are needed. We have proposed that sleep might be a default property of any simple neural network, which is modified by multiple other networks distributed throughout a complex nervous system. In vitro models (neural cultures, organotypic cultures, or slices) have long been used in the field of neuroscience with significant contributions to our understanding of basic mechanisms of central nervous system functions (e.g., long-term potentiation in hippocampal slices). More recently, human neurodevelopmental, neurodegenerative, and neuropsychiatric disorders are being modeled in vitro, either in rodent-derived primary neuronal cultures or human-derived neuronal induced pluripotent stem cells.[40-43]

In vitro evidence of the burst-pause neuronal discharge, characteristic of slow wave sleep, was first demonstrated using

dissociated rat cortical cultures.[44] This endogenous (default) discharge activity of neuronal networks has been verified in both organotypic explants[45,46] and dissociated neuronal cultures on multi-electrode arrays (MEAs),[47,48] leading to the proposal by Corner that the spontaneous burst discharges recorded in vitro are the basis of intrinsically generated slow wave sleep in vivo.[49] To extend these observations, Hinard and colleagues used mouse embryonic dissociated cortical cultures grown on MEAs and recorded their spontaneous discharge activity. The cellular responses to wake neuromodulators and the expression of plasticity-related genes as well as metabolic changes were measured.[50] Since cortical cultures invariably develop a burst-pause activity similar to the slow oscillation (<1 Hz) of NREM sleep, the challenge was to generate "wake-like" discharge activity. This has been achieved by applying a cocktail of known waking neuromodulators at physiologic concentrations. The chemical stimulation led to a desynchronized "wake-like" discharge activity, which was followed 24 hours later by the reappearance of the slow oscillation. Comparisons between baseline and recovery after in vitro stimulation with cortical tissues from living mice either at baseline or after sleep deprivation revealed a surprising similarity in terms of gene expression and metabolic changes.[50] This study and others, by using different techniques, convincingly demonstrated that the sleep-like state recorded in vitro is an emergent network property of mature neuron-glia cultures.[51,52]

In a parallel and complementary work by Jewett and colleagues, cultured cortical neurons and glia were stimulated by electrical, TNF, and optogenetic techniques.[51] Detailed analysis revealed that electrical stimulation led to the loss of synchronous burst-pause activity, which showed a homeostatic rebound (as measured by the slow wave power density) a day later, and this homeostatic response was stimulus pattern dependent.[51] On the contrary, addition of TNF to the cultures enhanced burstiness and synchrony, suggesting a deeper sleep-like state. The effects of IL-1, another sleep-promoting agent, was also investigated in the in vitro model of sleep.[53] Cultures from wild-type mice treated, whereas IL-1 showed enhanced slow wave activity, whereas cultures using cells from neuron-specific IL-1 accessory protein receptor knockout mice had delayed maturation in their spontaneous discharge activity, and delta activity following IL-1 treatment was not enhanced.[53] In another study, the homeostatic regulation of discharge activity in vitro was also demonstrated by neuromodulator stimulation at three different concentrations (mimicking different duration of enforced wakefulness in vivo).[54] The evidence that the emergent burst-pause network activity in vitro is identical to the slow oscillation (<1 Hz) of NREM sleep was confirmed by both local field potentials (LFP) and intracellular recordings.[55,56] Collectively, the in vitro work summarized previously is consistent with the hypothesis that small neuronal/glial networks manifest sleep-wake states that share properties similar to those of localized sleep within the cortex and whole animal sleep. One of the most important findings of in vitro studies is that continuous stimulation of neural networks cannot prevent the reemergence of the sleep-like state,[50,55] strongly confirming that the network stimulation (either by electrical or excitatory neuromodulators in vitro or by wakefulness in living animals) activates homeostatic processes to reestablish the default state sleep.

LOCAL MECHANISMS

Neuronal Circuit Mechanisms

The slow oscillation results from alternating synchronized active (up) and silent (down) states of cortical neurons and is locally generated and travels across cortical surface in an anteroposterior direction[57] not only during sleep in humans but also in cortical slices of ferrets.[58] As opposed to the slow oscillation, faster sleep oscillations such as delta waves (1 to 4 Hz) and spindles (10 to 15 Hz) require reciprocal interactions between the cortex and thalamus (and probably other subcortical structures). The frequency of cortical slow oscillation, slow waves, and spindles is modulated by thalamic inputs.[59,60] The generation of cortical spindles relies on interactions between thalamic reticular nucleus, thalamocortical relay projections, and corticothalamic feedback.[61] The thalamus is the major relay between arousal-promoting nuclei and the cortex and therefore is necessary to induce the waking active cortical state. Accordingly, optogenetic activation of the paraventricular glutamatergic neurons, centromedial, or ventromedial thalamic nucleus induces transitions from NREM sleep to wakefulness.[60,62,63]

So far, only the slow oscillation, as the characteristic feature of NREM sleep, was revealed in cultures of cortical and hippocampal neurons. Whether other sleep features can be recapitulated in vitro in thalamocortical co-cultures is under investigation. It is also not known if subcortical networks show locally similar or other features of sleep in vitro. The fact that the NREM sleep-like state is a default state even in species without a complex brain such as *C. elegans* strongly suggests that sleep is an emergent property of any neural network.[64] The enigma remains as to whether, similar to NREM sleep features, periodic desynchronization of cortical networks and associated muscle atonia and eye movements of REM sleep can also occur locally.

Local Use-Dependent Mechanisms Are Shared by Multiple Brain Processes Linked to Sleep

There are several linked brain physiologic processes that local cell use initiates. These include sleep, cerebral blood flow, inflammation, plasticity, and metabolism. Multiple molecules are produced and secreted in response to cell use, including nitric oxide (NO), adenosine triphosphate, adenosine, prostaglandins, IL-1, and TNF (Figure 31.1). These molecules dilate cerebral vessels, influence brain plasticity, and promote local inflammation and sleep.[23-25] Although all these processes are initiated by local events, the resultant changes manifest as emergent properties of higher, more complex levels of organization. For example, changes in local circuit plasticity may result in a new memory, or localized inflammation can lead to whole animal behavior, including sleep. Individual effector mechanisms for each process are, to a degree, compartmentalized partially because of the different cell types affected by local cell activation (e.g., neurons versus macrophages). Further, the higher-order emergent processes provide feedback in the forms of behavior, temperature, various dynamic electrochemical potentials, and so on to modify the initial cell-activation events. The mechanisms responsible for the higher-order emergent events begin at the cellular level and then diverge as the locally induced events merge, integrate, synchronize, and amplify into larger events as they climb up organizational levels.

BOX 31.2 MECHANISTIC HYPOTHESIS AND IMPLICATIONS FOR LOCAL USE-DEPENDENT SLEEP

Step 1: Cell activity (i.e., metabolism and electrical activity) induces synthesis and release of local sleep regulatory substances (SRS) (Figure 31.1) (*sleep is initiated locally*)
Step 2: SRS production is thus activity dependent (*sleep is homeostatically driven*)
Step 3: SRSs act locally to alter receptive, hence electrical, properties of nearby neurons and thus alter input-output relationships of the network within which they are found (*sleep is targeted to previously active networks*)
Step 4: The altered input-output network relationships reflect a functional state change (*sleep is local*)
Step 5: Sleep-like states in small local circuits synchronize with each other leading to organism state changes (*organism sleep is a network emergent property*)[a]
Step 6: Sleep regulatory circuits coordinate the individual network (e.g., cortical columns) functional states into organism sleep architecture (*sleep is adapted to the organism niche*)
Step 7: SRSs act on multiple levels of the neural axis to promote sleep (*sleep mechanisms are ubiquitous and evolutionarily ancient*)

[a]For a discussion of spontaneous synchronization, see Strogatz S. *Sync: The Emerging Science of Spontaneous Order*. Hyperion; 2003. For a mathematical model see Roy S, Krueger JM, Rector DM, Wan Y. Network models for activity-dependent sleep regulation. *J Theor Biol.* 2008;253:462–8.

However, regulation of sleep, inflammation, plasticity, cerebral blood flow, and metabolism are very difficult to separate experimentally from each other because of common local molecular initiating events. Thus among proposed sleep functions are plasticity, inflammation, metabolism, and cerebral blood flow. Further, most of the molecules mentioned also affect appetite, body temperature, and mood; it is proposed that modulation of these brain processes are also sleep functions. Thus, although it is understandable why these sleep functions have been proposed, the primordial sleep function must explain why reduced responsiveness to environmental cues (e.g., altered consciousness) is required.[65] As previously argued, circuit use–dependent plasticity/connectivity provides exceptional evolutionary fitness. Yet plasticity/connectivity involves changing local circuits, resulting in changes in circuit outputs to a given input. Thus the circuit output during waking is adaptive, presumed because the animal is alive, yet waking activity is causing the circuit to change via the actions of use-dependent molecules and thereby alters output to a given input. During such times, it would be advantageous if the animal were not behaving; unconsciousness would ensure such a reduced responsiveness state (i.e., sleep). Other proposed sleep functions could be accomplished with less risk without altering behavior. However, the synchrony of all the proposed use-dependent sleep functions within the rest phase would provide even greater evolutionary fitness.

Local to Global Hypotheses and Implications

Local events involved in the initiation of local network states eventually will manifest as whole organism sleep. The steps involved and their implications for sleep are briefly outlined in Box 31.2 (see the red type). There remains much work to fill in the details, especially determination of the timing of individual events and their relationship to the emergence and characterization of the various levels of organization involved (e.g., cellular–small networks–large networks–whole brain). In this chapter we focused on developing the hypothesis that small networks, whether in vivo or in vitro, display sleep-like properties.

CLINICAL PEARL

The use-dependent biochemical mechanisms responsible for local sleep are involved in multiple additional biologic processes, such as inflammation, cerebral blood flow, metabolism, and neuroplasticity. Sleep pathologies are likely to affect these processes. Further, localized sleep occurring during waking is likely linked to multiple clinical observations, such as insomnia, sleep inertia, dissociated states, poor performance, and excessive sleepiness. Finally, the local cerebral circuits involved in the perception of wakefulness remain active during sleep, and wakefulness may be perceived even though the patient is asleep as judged by other criteria, such as occurs during insomnia.[23,66,67]

SUMMARY

Ample historic evidence suggests that parts of the brain can be asleep while other parts are awake (e.g., sleepwalking, sleep inertia, dolphin unilateral sleep). Small networks, whether in vivo or in vitro, exhibit sleep-like properties, and that sleep within these networks is initiated by local cell activity has been hypothesized. Many, perhaps all, sleep regulatory molecules are locally synthesized in response to cell activity. Experimentally, local cortical sleep intensity can be increased or decreased by prior local activation or inhibition, respectively, whether achieved by enhanced or reduced localized afferent input, or by treatment with sleep regulatory substances or their inhibitors. Cortical columns oscillate between sleep- and wake-like states; behavior dependent upon a single cortical column is disturbed if the column is in the sleep-like state. Neuronal/glial co-cultures have a default sleep-like state, and their stimulation, electrically or chemically, is followed by enhanced expression of sleep regulatory substances and rebound sleep-like state indicating sleep homeostasis. The in vitro sleep-like state, like whole animal sleep, is also characterized by neuronal burstiness, synchrony of slow potentials, sleep-associated gene expression, and spontaneous reversibility. We conclude that small neuronal/glial networks constitute a minimal part of the brain capable of sleep states and that sleep-like states are the default state dependent upon prior cell use. This proposition provides greater explanatory parsimony of dissociated brain states, poor behavioral performance, insomnia, sleep-inertia, and other sleep anomalies and pathologies.

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A complete reference list can be found online at ExpertConsult.com.

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REVIEW QUESTIONS

1. Mixed mature cultures of glia and neurons exhibit which of the following characteristics?
   - **a.** Burstiness in neuron action potential firing
   - **b.** Sleep homeostasis
   - **c.** Can be driven into deeper sleep-like states with sleep promoting substances
   - **d.** Can be driven into wake-like states with excitatory substances
   - **e.** All of the above

2. Evidence suggesting that different parts of the brain can simultaneously be awake and asleep includes:
   - **a.** Unilateral sleep in marine mammals and birds
   - **b.** Oscillating amplitudes of slow potentials in cortical islands
   - **c.** Oscillations between REMS and NREMS in humans
   - **d.** Rapid electrical stimulation of almost any part of the brainstem induces sleep
   - **e.** A and B only

3. Evidence supporting the hypothesis that local areas of brain oscillate between sleep- and wake-like states includes:
   - **a.** After intensive stimulation of afferent neuron activity, the cortical areas receiving the enhanced input in subsequent sleep exhibit enhanced electroencephalogram (EEG) delta wave activity.
   - **b.** After reduced stimulation of afferent neuron activity, the cortical areas receiving the reduced input in subsequent sleep exhibit reduced EEG delta wave activity.
   - **c.** Cortical columns oscillate between wake- and sleep-like states.
   - **d.** In rats, the error rate in a learned behavior task dependent upon the input to a single cortical column involved in the learned task is increased if the cortical column is in the sleep-like state.
   - **e.** All of the above

4. Molecules released in brain as a consequence of cellular activity:
   - **a.** Include nitric oxide, adenosine triphosphate, adenosine, cytokines, and neurotrophins
   - **b.** Often alter both sleep frequency/duration and synaptic plasticity
   - **c.** Act locally within the circuits where they are released to affect sleep-like states
   - **d.** A, B, and C
   - **e.** B and C only

ANSWERS

1. **E**

2. **E**

3. **E**

4. **D**