[Frontiers in Bioscience 8, d511-519, May 1, 2003]

SLEEP FUNCTION

James M. Krueger [1] and Ferenc Obal Jr. [2]

[1] Department of Veterinary and Comparative Anatomy, Pharmacology, and Physiology, Washington State University, Pullman, WA 99164-6520, [2] Department of Physiology, University of Szeged, A. Szent-Györgyi Medical Center, 6720 Szeged, Hungary

TABLE OF CONTENTS

1. ABSTRACT

A theory of sleep function and brain organization positing that sleep serves a neuronal connectivity function and is a fundamental property of highly interconnected groups of neurons (neuronal groups) is presented. Cellular electrical activity within neuronal groups leads to the production of sleep-promoting substances which are also cytokine growth factors. The somnogenic cytokine growth factors (SCGF) in turn, induce molecules necessary for synaptic connectivity. The SCGFs change the synaptic activation patterns within neuronal groups. SCGFs thus induce changes in the input-output relationships of neuronal groups and thereby, cause a neuronal group state shift. Altered input-output relations result in increased efficacy of some synapses. Sleep is thus, targeted to active neuronal groups and serves to incorporate novel stimulus patterns into a synaptic contextual network and also to preserve that network. Coordination of neuronal group state is brought about by sleep regulatory networks. Organism sleep is an emergent property of a population of neuronal groups in the sleep state. After the neuronal group state shift, environmental input is divorced from output. Sleep is thus, useful to keep the animal stationary at a time when its brain is most dysfunctional. Thus, not only is unconsciousness needed because output activity would be out of phase with environmental events, but it is the consequence of the process itself.

2. INTRODUCTION

Most people recognize the importance of sleep and are aware of the cognitive and physical dysfunction that accompanies sleep loss. Patients suffering from primary and secondary sleep disorders and their physicians are even more keenly aware of the associated performance detriments. The understanding of sleep is also one of the most important problems confronting neurobiology because the reasons why we sleep remain unknown. It seems likely that if we are ever to understand waking functions such as memory, perception, emotion, thought, etc, we will have to first provide an experimentally verified function for sleep. Further, an understanding of how the brain is organized to produce sleep will likely help solve questions as to how the brain achieves waking functions. In this essay, we address brain organization of sleep and sleep function; we view these two subjects as inseparable. It is our opinion that solutions to these problems are now near at hand within the grasp of the experimental neurobiologist. These issues are thus important, timely and almost irresistible to think about.

There are many theories of sleep function (e.g. see 1). These theories fall into two broad categories; neuronal connectivity theories and bodily theories. Neuronal connectivity theories suggest that sleep serves to maintain, consolidate or repair synapses and the neuronal circuits within which they function. The bodily theories focus on extra-cranial functions of sleep such as restoration of energy stores (reviewed 2). Unfortunately, all of the bodily theories and most of the neuronal connectivity theories fail to explain an indispensable and defining feature of sleep; the reduction of environmental responsiveness (unconsciousness). Superficially, unconsciousness is maladaptive since, while asleep, one does not eat, drink, socialize or reproduce and one is more subject to predation. Thus whatever the need for sleep, it must be greater than these apparent disadvantages associated with unconsciousness. Sleep could, of course, serve more than one function (see below), however, it seems likely to have initially evolved to serve a primordial function not yet experimentally identified.

A number of sleep function theories, beginning with Moruzzi's (3), invoke the idea that sleep serves a

function for the synapse (reviewed 4). In fact, if we include in this category the sleep theories postulating that sleep serves a memory function (e.g., 5, 6, 7, 8, 9), and those hypothesizing that sleep helps information processing (e.g., 1) and those positing that sleep serves developmental connectivity (10, 11) plus those directly stating that sleep affects synapses (e.g. 12, 13, 14, 15), the theories appear to converge on the general hypothesis that sleep is needed for alterations in neuronal connectivity to occur or solidify. It is our opinion, however, that all of these theories, except one (12) ignore the issue of how sleep mechanisms lead to unconsciousness. Regardless, over the past 30 years many eminent and thoughtful sleep researchers have reached the conclusion that sleep has something to do with neuronal connectivity. We thus now briefly consider characteristics and mechanisms of neuronal connectivity in order to develop ideas as to mechanisms and functions of sleep.

A fundamental tenet of neurobiology is that neural circuitry activation is responsible for brain outputs such as perception, thought, etc. This circuitry is anatomically defined by synapses in what is referred to as the brain microcircuitry. Another fundamental tenet of neurobiology is that the microcircuitry is in constant flux, even in adults, and that changes in the microcircuitry (plasticity) are responsible for the incorporation of new memories, integration of new experiences into old, motor coordination etc. There is a large and rich literature dealing with many forms of plasticity, (e.g. 16). Many biochemical and morphological mechanisms are used to alter neurotransmission. Such changes take place over different time frames ranging from milliseconds (e.g. paired-pulse facilitation), to seconds and minutes (e.g. long term potentiation) and hours to a lifetime (e.g. learned tasks such as motor coordination) (17). The latter two categories of plasticity involve protein synthesis and gene expression.

A third tenet of neurobiology logically flows from the first two mentioned here. Synaptic activation leads to targeted modifications in synaptic transmission, and thus connectivity, and these changes are responsible for alterations in synaptic efficacy (the ease of electrical [neurochemical] transmission through a synapse). The resulting microcircuitry modifications thus alter a circuit's output in response to a given input. These changes are dependent upon cell activation and are referred to as activity- or use-dependent changes. Targeting these activity-dependent changes to specific synapses requires a variety of strategies. Thus, neurons use at least two approaches for use-dependent regulation of protein synthesis and synapse targeting (reviewed 17). In activated cells, proteins are translated from newly transcribed mRNAs in the soma. For instance cAMP response element binding protein (CREB), a transcription factor, is activated in response to synaptic stimulation (18). Second, mRNAs are transported to activated synapses where they are translated (e.g. activity-related cytoskeletal protein [arc]) (19, 20). Some mRNAs are localized to synapses (e.g. microtubule-associated protein-2) (21) and dendritic shafts contain the machinery necessary for translation, e.g. polyribosomes, initiation factors, etc. How changes in membrane potential turn on the translation processes at the specific activated synapse remains to be completely described but likely involves changes in cytosolic calcium and perhaps substances such as cytoplasmic polyadenylation element binding protein (22). This research area remains one of the most intense and important in neurobiology since it is aimed at the mechanisms responsible for some of the fundamental tenets of neurobiology.

Neurotrophins such as nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) are regulatory molecules whose expression in neurons is activity-dependent (reviewed 23). The neurotrophin hypothesis posits that activity-dependent regulatory molecules, e.g. NGF, BDNF, participate in neural plasticity. Cellular electrical activity alters the synthesis and actions of these regulatory molecules and they, in turn, directly alter electrical properties of cells containing their receptors and alter the expression of countless molecules necessary for synaptic efficacy and plasticity. Such actions are well known for neurotrophins such as NGF and BDNF (reviewed 21, 23, 24). Many neurotrophins are also considered cytokines for instance, NGF and BDNF, and similar actions are also exhibited by other cytokines, such as tumor necrosis factor alpha (TNF alpha), a substance implicated in sleep regulation (25). TNF alpha, its receptors and signaling pathways are constitutively expressed in the CNS and can be expressed in glia and neurons (reviewed 26). The synthesis of TNF alpha is enhanced by neural activity (27, 28). TNF alpha in turn enhances expression of AMPA receptors (a class of glutamate receptors) and thereby affects input-output relationships of neurons (29) and cytosolic calcium levels (30). These actions of TNF alpha appear to be physiological in the sense that an inhibitor of TNF alpha, the soluble TNF receptor, inhibits AMPA-induced postsynaptic potentials (29) and AMPA-induced changes in cytosolic calcium (30). AMPA receptors play a key role in synaptic plasticity (reviewed 31, 32). Consequently, TNF alpha plays a direct role in sleep regulation and an indirect role in synaptic plasticity.

Thus far we have gone quickly from acknowledging that sleep researchers hypothesized a plasticity function for sleep to general cellular and molecular mechanisms of plasticity and how one putative sleep-regulatory substance, TNF alpha, affects plasticity. The plasticity-related molecules used thus far as examples are substances that are either affected by sleep [CREB (33), arc (34), BDNF (35), TNF alpha (36) and/or directly affect sleep [NGF (37), BDNF (38), TNF alpha (39)]. Before proceeding to a sleep theory that incorporates what we know about plasticity into a mechanistic hypothesis of sleep, we first need to take a step back and address a larger issue, the need for changes in neuronal connectivity, and how that need impacts sleep mechanisms.

Complex information processing creates obvious evolutionary advantages. It seems reasonable to propose that the evolution of complex ganglia/brains might occur by either greatly increasing the total number of neurons in circuits dictated by genetics (as in the evolution of

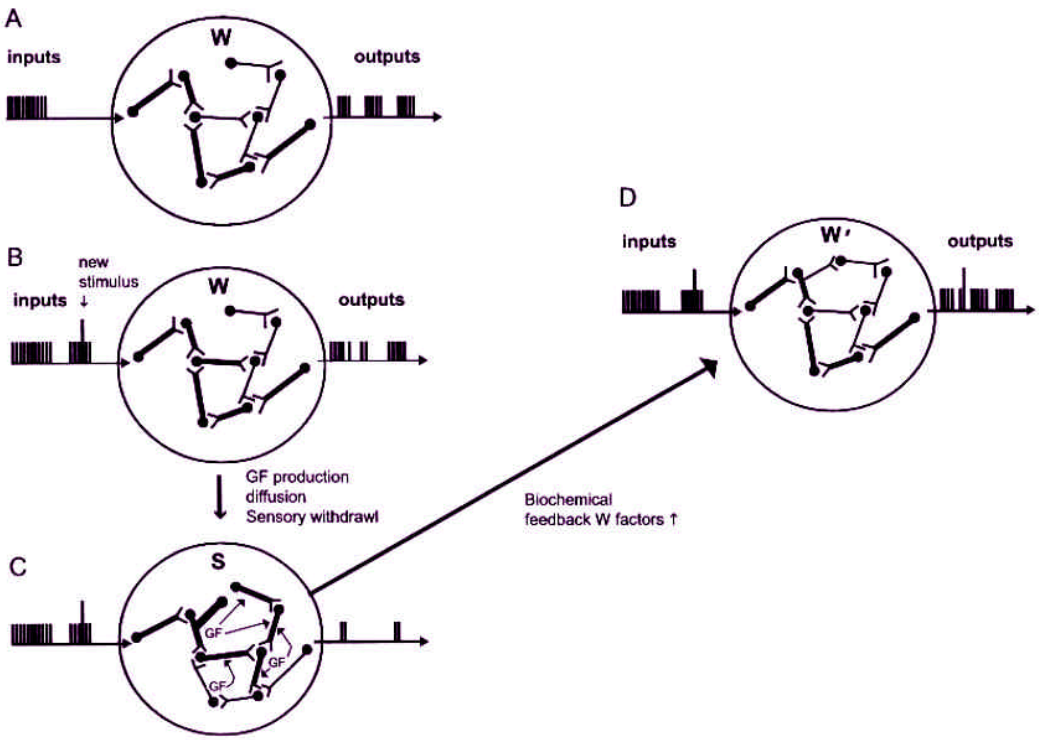

Figure 1. State shifts within neuronal groups provide a way to preserve a contextual framework within which new stimuli need to be integrated. The waking state (W) of a neuronal group is characterized by input-output relationships (top A). If a new stimulus is introduced, input-output relationships are different (B). Inputs induce production of SCGFs that alter the electrical properties of nearby neurons and thereby alter input-output relationships (C). The altered state can be considered sleep (S) (see text). The SCGFs induce long-term changes in connectivity within a neuronal group thereby incorporating new experience patterns into the old (D). Thus, the novel stimulus illustrated induces changes in the network via activity-dependent synthesis of regulatory molecules involved in synaptic efficacy. These substances, via paracrine actions, also preserve the efficacy of nearby synapses via their ability to induce altered membrane electrical properties of the affected neurons. The input-output relationships of the neuronal group are thus altered. It is posited that in one state, the neuronal group possesses input-output relationships that are environmentally relevant while in the activity-dependent SCGF-induced state the input-output relationships no longer have direct bearing to the environment. The latter state could thus be considered a sleep state because environmental stimuli no longer induce an environmentally relevant response. Unconsciousness results when sufficient numbers of neuronal groups are in this state.

computers) or by involving single neurons in multiple flexible circuits (shared use). In both scenarios the connection complexity would rapidly outgrow the informational content available in genetic material. Choosing the strategy of increasing the total neuron number would result in severe spatial and metabolic limits. The shared use of neurons in multiple circuits seems a more advantageous design since the ganglionic load could be reduced for the same amount of processing ability. However, the penalty for this strategy is the development of epigenic plasticity and rules of connectivity between neurons that are use-dependent (40). Such a strategy would result in a reduced metabolic load for the "information processor" and allow for flexibility by incorporating epigenic experience-driven lessons into the processor.

However, such a plan presents another problem; the preservation of useful synapses and circuits. The fact that an organism lives is *prima facie* evidence that its processor already has useful circuits that have ensured survival. How does it incorporate new useful circuits/synapses into the already present, proven adaptive, circuits? In other words, "new" information needs to be incorporated within a contextual framework while simultaneously preserving the "old". Consequently, organisms must stabilize the old, incorporate the new, and target both processes to activated networks.

3. STATE SHIFTS WITHIN A GROUP OF HIGHLY INTERCONNECTED NEURONS

As synapses and circuits are used there is the induction and release of somnogenic cytokines/growth factors (SCGFs) that are responsible for synaptic sculpturing (the neurotrophin hypothesis). In an autocrine fashion, these activity-dependent substances alter synaptic efficacy via nuclear transcription events and translation mechanisms targeted to the specific synapses that were activated. They also act in a paracrine fashion to affect the electrical properties of nearby neurons such that a given input results in a different output (see Figure 1). Within a group of highly interconnected neurons (hereafter called neuronal groups), the SCGF-induced altered input-output relationships can, by definition, be considered a state shift.

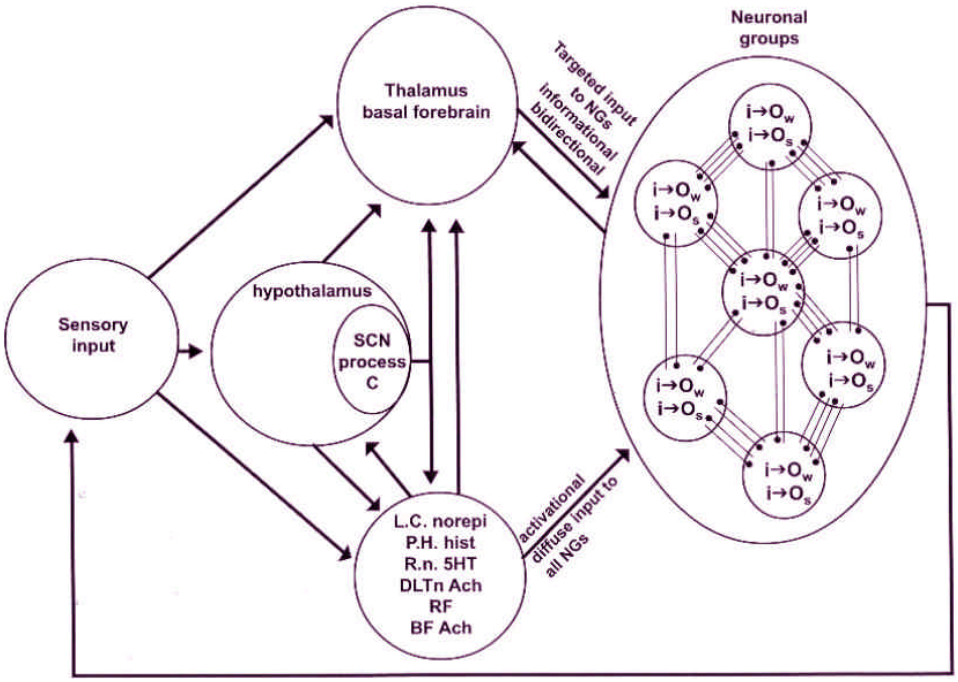

Figure 2. Sleep regulatory networks and activational circuits involved in the coordination of neural group (NG) state. Individual neuronal groups (right) oscillate between waking (w) and sleep (s) states depending upon their prior activity. Neuronal groups in proximity to each other tend to map onto each other (- - •) and thereby tend to phase-lock states with each other. Sleep regulatory networks (thalamus/basal forebrain – top middle) have bi-directional connections with the neuronal groups and help in the coordination of the sleep states of the neuronal groups with autonomic and somatomotor functions associated with sleep. The activational circuits (middle bottom) extensively map onto neuronal groups throughout the cortex and serve to phase-unlock the neuronal groups (see text). Higher level regulatory circuits (e.g. hypothalamus) are also involved in balancing the actions of the thalamic and basal forebrain circuits and the activational circuits. See the chapters by Szymusiak and McGinty, Steride, Zabroszky and Duque, Semba and Deurvilher, and Jones in this volume for an in depth discussion of sleep regulatory networks. *Abbreviations*: SCN, suprachiasmatic nucleus; LC, locus ceruleus; PH, posterior hypothalamus; RN raphe nucleus; DLTn, dorsal lateral tegmentum nucleus; RF, reticular formation; BF, basal forebrain. $i \rightarrow o_w$ represents input-output during waking while $i \rightarrow o_s$ represents sleep.

It is well known that a variety of SCGFs such as interleukin-1 beta (IL1 beta), TNF alpha, NGF and BDNF alter either the responsiveness of neurons to stimuli or directly stimulate changes in membrane potentials (reviewed 24, 41). These actions of SCGFs on membrane potentials have two important manifestations. First, such actions result in the use of synapses that heretofore were not activated by the particular stimulus; this action would in turn trigger, with a delay, the molecular events which maintain synaptic efficacy of those newly activated synapses and the consolidation of recently formed synapses. We consider this a function of sleep (12); i.e. the preservation of synapses insufficiently activated by afferent input during wakefulness, yet which are essential for providing a contextual framework. Second, the SCGFs induced in activated neuronal groups would, due to diffusion, biochemical reaction times and regulatory feedback loops, result in neuronal group electrical and biochemical oscillations (12). The SCGF-induced altered input-output relationship, or state shift, can be considered a sleep state since after the state shift environmental input no longer elicits environmentally-relevant outputs. For instance, if the initial conditions are such that environmentally driven inputs induce adaptive outputs (waking) then a shift in input-output relationships could result in outputs lacking the necessary connectivity to induce coordinated mental or motor patterns. Thus, individual neuronal groups are alternating between states, one in which input induces environmentally-relevant output and one in which it does not. In addition, while oscillating between states, novel stimulus patterns are incorporated into a contextual framework and the synapses responsible for the contextual framework are preserved.

4. GOING GLOBAL WITH NG STATE SHIFTS TO ORGANISM SLEEP

Sleep is a global behavioral phenomenon. Thus, the sleeping mode of neuronal groups needs to be coordinated and effector mechanisms that bring about the somatomotor and autonomic changes normally associated with sleep have to be engaged. There are two mechanisms responsible for coordination of neuronal groups. The first is a consequence of the topographical organization of the cerebral cortex. For example, within the somatosensory cortex of rats, individual barrels, which are involved in processing information from a single facial whisker, tend to map onto each other and the extent of mapping is greater the closer barrels are to each other (Figure 2). The action potentials from one neuronal group to an adjacent neuronal

group would tend to phase-lock the states of the neuronal groups to each other and thereby induce local synchronization of neuronal group state within the somatosensory cortex. Such coordination mechanisms would function in sleep and wake states although the precise patterns of mapping would be different between states. Sleep regulatory networks would also be involved in coordination of neuronal group state and with the engagement of circuits involved in autonomic and somatomotor changes associated with sleep. There are two basic features that these networks need to possess. They have to receive inputs from neuronal groups all over the brain and they need to be able to modulate activities of neuronal groups dispersed in distant parts of the brain. These are, in fact, characteristics of the projection neurons in the thalamus and basal forebrain (figure 2). Finally, these two coordinating mechanisms would in some instances also affect electroencephalogram (EEG) frequencies leading to perhaps those patterns characteristic of sleep and binding mechanisms.

The role of the sleep regulatory networks can be envisioned as follows. Sleep need is conveyed to these neurons by the SCGF-induced altered activity of neuronal groups through the bi-directional pathways between the cortical neuronal groups and the thalamus (i.e. corticothalamic pathways) and the basal forebrain (i.e. cortical neurons projecting to the cholinergic and non cholinergic basal forebrain neurons) (figure 2). The various activational circuits are also involved in the coordination of neuronal group sleep states. Thus, because of their far reaching projections and activating actions they could serve to reverse the tendency of neuronal groups to phase-lock with each other. An interesting aspect of such an arrangement is that each of the activational networks could work independently using different transmitter and mapping mechanisms on the circuitry of the neuronal groups and thereby add to the richness and complexity of waking states.

Further, as sleep regulatory networks begin to modulate the activity of significant neuronal group numbers, sleepiness is perceived and normal preparative sleep behavior ensues. The sleep regulatory networks are also capable of mediating sleep-promoting stimuli arising from the body or specific neural structures. Thereby through these networks sleep can serve secondary functions that have co-evolved with the primary plasticity function (thermoregulation, host defense, caloric savings and conveying circadian input from the suprachiasmatic nucleus).

5. THE NEED FOR SLEEP

It seems logical that if activity-dependent SCGFs induce altered input-output relationships and the neuronal group states shift such that environmental input is functionally divorced from neuronal group output then behavioral abnormalities would ensue. Cognitive and physical performance dysfunction (as well as many others), in fact, occur with sleep loss and such problems become progressively worse (42). Further, waking state stability becomes more fragile as sleep loss persists, e.g., the probability of lapses into microsleep increases (42). Prolonged wakefulness is likely accomplished, in part, by use of the activational systems to keep neuronal groups in an “awake” state. This would result in even more intense neuron use within the affected neuronal groups thereby causing an even greater synthesis of use-dependent SCGFs, which would tend to increase the propensity to jump into the “sleep” state. Thus with progressive sleep loss the activity of two opposing neuronal group-state determining mechanisms (activation circuits and SCGF production) would increase. This is the equivalent of greatly increasing the gain of a regulated system and thereby increasing instability (high gain-induced amplified error around a set point).

Within a population of neuronal groups, as wakefulness becomes prolonged, the fraction of neuronal groups, either switching to the “sleep” mode or progressively becoming more unstable due to turning up the gain would increase. At some point, a predicted emergent property of the system (brain) would be a system-wide state shift. This emergent property would be associated with unconsciousness since a large fraction of the neuronal groups would be in a state where environmental input is divorced from a functional output. It would also be advantageous to prevent physical activity of the animal at a time when its brain is most dysfunctional. Thus, unconsciousness is needed not only because output activity would be out of phase with environmental input, but also because it is the consequence of the process itself (43).

6. SLEEP HOMEOSTASIS; IMPLICATIONS FOR SLEEP FUNCTION

Sleep is homeostatically regulated in the sense that sleep loss induces an increased sleep propensity and that sleep duration and intensity increase after sleep deprivation. Benington (44) has emphasized that the functions of other homeostatically regulated processes are directly related to their homeostatic control mechanisms. Currently, there is extensive information concerning the biochemical regulatory mechanisms of sleep (see Obal and Krueger, this volume). Several characteristics of sleep regulatory substances are consistent with the idea that sleep serves a synaptic function. For instance, neuronal use stimulates the production release of many sleep regulatory substances, e.g. TNF alpha (see above), nitric oxide, adenosine, NGF, BDNF, IL1. Mechanistically, this suggests that sleep is related to prior neuronal activity rather than wakefulness *per se.* In addition, since these substances cause sleep when administered to an animal or when upregulated endogenously, it logically follows that sleep is related to synaptic activity. We can also ask: What types of activity are these sleep regulatory substances involved in? In fact, that these substances are involved in synaptic plasticity mechanisms suggests that sleep is involved as well. Sleep thus would be predicted to affect molecules known to be involved in plasticity, although conversely such molecules need not be involved in sleep regulation directly. Many such molecules are affected by

sleep loss, e.g. arc (34, 45), metalloproteinase-9 (34), tissue plasminogen activator (34), trk B (35), glutamate decarboxylase (46). In conclusion, our knowledge of the biochemical mechanisms responsible for sleep is consistent with a role for sleep in synaptic plasticity.

Another facet of sleep regulatory mechanisms deals with the sleep regulatory circuits (e.g. see figure 2). Indeed, most sleep mechanisms studies have focused on such networks as the preoptic/basal forebrain for non-rapid eye movement sleep or on pontine rapid eye movement sleep circuits or on the various activational networks. These networks are indeed involved in sleep regulation and, as mentioned above, they are posited to affect activity within neuronal groups and to be involved in the coordination of neuronal group states. However, it is the regulated variable that gives a clue for sleep function, not the specific neuronal circuit involved.

7. IMPLICATIONS AND PREDICTIONS OF THE THEORY; EXPERIMENTAL SUPPORT

A fundamental postulate of this theory is that sleep is a property of neuronal groups and that organism sleep is a statistical function of the number of neuronal groups in the sleep mode (12). Thus, one would anticipate that parts of the brain could be asleep while other parts are awake. This indeed is characteristic of dolphin sleep; dolphins never exhibit the high amplitude EEG slow waves associated with non-rapid eye movement sleep on both sides of the brain simultaneously (47). Further, if only one side of the brain is deprived of sleep, that side but not the contralateral side, shows sleep rebound (48). As humans enter sleep, EEG slow wave activity occurs first, and is more intense, in the frontal cortex than in the occipital cortex (49). Cerebral blood flow measurements also clearly demonstrate regional differences during sleep or sleep loss (50, 51, 52). Clinical observations in stroke patients suggest that wakefulness and sleep occur simultaneously in different parts of the brain (53). On a cellular level, as an animal is beginning to enter sleep, some neurons of the visual association cortex display characteristic sleep firing patterns even when the animal is performing a visual discrimination task (54). Mid-pontine transection of the cat brain results in the generation of a rapid eye movement sleep-like state in the brain stem while the disconnected forebrain waxes and wanes in and out of EEG synchronization (55). EEG slow wave activity of isolated cortices (56; reviewed 57) in otherwise intact animals, also waxes and wanes thereby suggesting that intrinsic activity of the cortex can induce oscillatory field potentials. Countless lesion/stroke studies suggest that regardless of the lesion location, if the animal survives, sleep always occurs (reviewed 2). Finally, slow electrical stimulation of many brain areas induce EEG synchronization (reviewed 57). Collectively, such data strongly suggest that there is no common pathway necessary for sleep or EEG synchronization and that much of the encephalon has hypnogenic properties (58).

Another facet of the theory is that sleep is dependent upon prior neuronal use. Thus, one would predict that if a part of the brain were disproportionately activated, then in subsequent sleep that part of the brain would exhibit a higher intensity of sleep. Indeed, the first experimental test of the theory demonstrated this phenomenon. Kattler *et al* (59) excessively stimulated the right hand of volunteers during wakefulness, during subsequent sleep increased EEG delta power was observed in the left cortex [EEG delta power reflects sleep intensity (reviewed 60)]. In later studies by the same group, similar results were obtained from rat somatosensory cortex after unilateral facial whisker removal and sleep deprivation; the side ipsilateral to the cut whiskers thus received disproportionate sensory stimulation and it exhibited enhanced EEG delta power in subsequent sleep (61). Similar results were obtained in another study using acollasal mice (62). Additional reports suggest the idea that sleep is targeted to areas depending upon their prior activity. For instance, Maquet (51) concluded that the intensity of sleep is targeted to specific areas of brain depending upon prior use.

A third general prediction of the theory is that any brain function dependent upon plasticity should be sensitive to sleep. Steriade (63) has suggested that the neuronal activity of cortico-cortical circuits associated with non-rapid eye movement sleep promotes synaptic plasticity. There are several developmental studies consistent with the notion that the characteristic high plasticity of the development period is affected by sleep and /or sleep loss. Higher levels of SCGFs in the developing brain, could partially account for the greater amounts of sleep and plasticity during development. In the developing human brain, frontal cortex synaptic density correlates with increased EEG delta activity (64). In cats, rapid eye movement sleep deprivation enhances the effects of monocular deprivation on the cell size of lateral geniculate neurons (11). Another more extensive study using a similar animal model, showed that sleep as well as sleep loss modified cortical plasticity (10). Memory is also posited to be dependent on synaptic plasticity and sleep. In the developing chick, left hemisphere sleeping is linked to fixation of memories developed during waking activities (65). There are also many reports of mammalian hippocampal-dependent memory being sleep dependent. In a series of studies, Smith (6) has shown that sleep during a critical window after learning a task is necessary for retention of the learned task. Sleep is also required to learn new visual discrimination tasks (9) and motor tasks (66). Sleep loss also greatly inhibits hippocampal long-term potentiation (67). Finally, previously we had predicted (43) that sleep loss should affect neurogenesis; Guzman-Marin *et al* (68) recently provided evidence in support of this prediction.

8. PERSPECTIVE

Sleep most likely serves multiple functions although it probably evolved to serve some primordial function such as synaptic plasticity as argued here (12). Sleep is important, if for no other reason than it occupies such a large fraction of each day in most species. For neurobiology, its importance lies in the high probability that we must fully understand what sleep does for the brain

before we can decipher the mechanisms responsible for higher brain functions. There are now many good proposals for sleep function and they are beginning to be tested experimentally. It is thus an exciting time to be in sleep research. In the past, there has been much spirited debate over the issue of sleep function. In the future, the discussion will continue and intensify with one major difference, now we can begin to bring experimental evidence to the arena of intellectual debate.

9. ACKNOWLEDGMENTS

We thank Dr. Steven Simasko, Danielle Nelson, and Deborah Duricka for their help with this manuscript. This work was supported by the National Institutes of Health, grant numbers NS25378, NS27250, NS31453 and HD36520.

10. REFERENCES

1. Giuditta A: The function of sleep. *Behav Brain Res* 69, 1-218 (1995)

2. Krueger JM, F. Obál Jr., L. Kapás & J. Fang: Brain organization and sleep function. *Behav Brain Res* 69, 177-185 (1995)

3. Moruzzzi G: The sleep-waking cycle. *Rev Physiol* 64, 1-165 (1972)

4. Krueger JM, F. Obál Jr. & J. Fang: Why we sleep: A theoretical view of sleep function. *Sleep Med Rev 3*, 119-129 (1999)

5. Crick F, G. Mitchinson: The function of dream sleep. *Nature* 304, 111-114 (1983)

6. Smith C: Sleep states, memory processes and synaptic plasticity. *Behav Brain Res* 78, 49-56 (1996)

7. Davis B: Sleep and the maintenance of memory perceptives. *Biol Med* 28, 457-464 (1985)

8. Poe GR, Nitz DA, McNaughton BL & Barnes CA: Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Res* 855, 176-180 (2000)

9. Stickgold R, L. James & J.A. Hobson: Visual discrimination learning requires sleep after training. *Nat Neurosci* 3, 1237-1238 (2000)

10. Frank MG, N.P. Issa & M.P. Stryker: Sleep enhances plasticity in the developing visual cortex. *Neuron* 30, 275-287, (2001)

11. Marks GA, J.P. Shaffery, A. Oksenberg, S.G. Speciale & H.P. Roffwarg: A functional role for REM sleep in brain maturation. *Behav Brain Res* 69, 1-11 (1995)

12. Krueger JM & F. Obál Jr.: A neuronal group theory of sleep function. *J Sleep Res* 2, 63-69 (1993)

13. Kavanau JL: Memory, sleep, and dynamic stabilization of neural circuitry: Evolutionary perspectives. Neurosci *Biobehav Rev* 20, 289-311 (1996)

14. Kavanau JL: Origin and evaluation of sleep: Roles of vision and endothermy. *Brain Res Bull* 42, 245-264 (1997)

15. Benington JH, HC Heller HC: Restoration of brain energy metabolism as the function of sleep. *Prog Neurobiol* 45, 347-360 (1995)

16. Baudry M, J.L. Davis, R.F. Thompson. Advances in Synaptic Plasticity. The MIT Press, Cambridge (2000)

17. Wells DG, J.D. Richter & J.R. Fallon: Molecular mechanisms for activity-regulated protein synthesis in the synapto-dendritic compartment. *Curr Opinion Neurobiology* 10, 132-137 (2000)

18. Alberini CM, M. Ghiradi, R. Metz & E.R. Kandel: C/EBP is an immediate-early gene required for the consolidation of long-term facilitation of Aplysia. *Cell* 76, 1099-1114 (1994)

19. Link W, U. Konietzko, G. Kauselmann, M. Krug, B. Schwanke, U. Frey & D. Kuel: Somatodendrite expression of an immediate early gene is regulated by synaptic activity. *Proc Natl Acad Sci USA* 92, 5734-5738 (1995)

20. Lyford GL, K. Yamagata, W.E. Kaufmann, C.A. Barnes, L.K. Sanders, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, A.A. Lanahan & P.F. Worley: Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron* 14, 433-445 (1995)

21. Vaillant AR, P. Zanassi, G.S. Walsh, A. Aumont, A. Alonso & F.D. Miller: Signaling mechanisms underlying reversible, activity-dependent dendrite formation. *Neuron* 34, 985-998 (2002)

22. Wu L, D. Wells, J. Tay, D. Mendis, M.A. Abbott, A. Barnitt, E. Quinlan, A. Heynen, J.R. Fallon & J.D. Richter: CPEB-mediated cytoplasmic polyadenylation and the regulation of experience-dependent translation of alpha-CaMKII mRNA at synapses. *Neuron* 21, 1129-1139 (1998)

23. Schinder AF & M.-M. Poo: The neurotrophin hypothesis for synaptic plasticity. *TINS* 23, 639-645 (2000)

24. Zhang LI & M.-M. Poo: Electrical activity and development of neural circuits. *Nature* 4, 1207-1214 (2001)

25. Krueger JM, Obál F. Jr., J. Fang, T. Kubota & Taishi P: The role of cytokines in physiological sleep regulation. *Ann NY Acad Sci* 933, 211-221 (2001)

26. Majde JA & J.M. Krueger: Neuroimmunology of sleep. In: Biological Psychiatry. Eds D'haenen H, den Boer JA & Willner P, John Wiley & Sons Ltd, (2002)

27. De Bock F, J. Dornand & G. Rondouin: Release of TNF alpha in the rat hippocampus following epileptic seizures and excitotoxic neuronal damage. *Neuroreport* 7, 1125-1129 (1996)

28. De A, S.M. Simasko & J.M. Krueger: Effects of glutamate on the expression of tumor necrosis factor alpha in cultures of hypothalamic cells. *Sleep* 24, A150 (2001)

29. Beattie EC, D. Stellwagen, W. Morishita, J.C. Bresnahan, B.K. Ha, M. Von Zastrow, M.S. Beattie & R.C. Malenka: Control of synaptic strength by Glial TNF alpha. *Science* 295, 2282-2285 (2002)

30. De A, S. Simasko & J.M. Krueger: TNF alpha increases intracellular calcium responses to KCl and AMPA in primary cultures of fetal hippocampal neurons. *Soc Neurosci Abst* 26, 1363 (2000)

31. Malinow R & R.C. Malenka: AMPA receptor trafficking and synaptic plasticity. *Ann Rev Neurosci* 25, 103-126 (2002)

32. Luscher C & Frerking M.: Restless AMPA receptors: Implications for synaptic transmission and plasticity. *Trends Neurosci* 24, 665-670 (2001)

33. Hendricks JC, J.A. Williams, K. Panckeri, D. Kirk, M. Tello, J.C. Yin & A. Sehgal: A non-circadian role for cAMP signaling and CREB activity in Drosophila rest homeostasis. *Nat Neurosci* 4, 1108-1115 (2001)

34. Taishi P, C. Sanchez, Y. Wang, J. Fang, J.W. Harding & J.M. Krueger: Conditions that affect sleep alter the expression of molecules associated with synaptic plasticity. *Am J Physiol Reg Integ Comp Physiol* 281, R839-R845 (2001)

35. Cirelli C: Functional genomics of sleep and circadian Rhythm, Invited Review: How sleep deprivation affects gene expression in the brain: A review of recent findings. *J Appl Physiol* 92, 394-400 (2002)

36. Floyd RA & J.M. Krueger: Diurnal variations of TNF alpha in the rat brain. *NeuroReport* 8, 915-918 (1997)

37. Takahashi S & J.M. Krueger: Nerve growth factor enhances sleep in rabbits. *Neurosci Lett* 264, 149-152 (1999)

38. Kushikata T, J. Fang & J.M. Krueger: Brain-derived neurotrophic factor enhances spontaneous sleep in rats and rabbits. *Am J Physiol* 276, R1334-1338 (1999)

39. Shoham S, D. Davenne, A.B. Cady, C.A. Dinarello & J.M. Krueger: Recombinant tumor necrosis factor and interleukin 1 enhance slow-wave sleep. *Am J Physiol* 253, R142-R149 (1987)

40. Edelman GM: Neural Darwinsim. Basic Books, New York (1987)

41. Shibata M: Hypothalamic neuronal responses to cytokines. *Yale J Biol Med* 63, 147-156 (1990)

42. Doran SM, H.P. Van Dongen & D.F. Dinges: Sustained attention performance during sleep deprivation: Evidence of state instability. *Arch Ital Biol* 139, 253-267 (2001)

43. Krueger JM & F. Obál Jr: Function of sleep. In: Sleep Medicine. Eds: Lee-Chiong TL, MJ Sateia, MA Carskadon, Hanley & Belfus, Philadelphia PA, 23-30 (2002)

44. Benington JH: Sleep homeostasis and the function of sleep. *Sleep* 23, 959-966 (2000)

45. Cirelli C & G. Tononi: Sleep, waking and neural plasticity: New insights from the expression of P-CREB, BDNF and Arc across the sleep-waking cycle and after sleep deprivation (Abstract). *Sleep* 23, A61 (2000)

46. Churchill L, P. Taishi, Z. Guan, L. Chen, J. Fang & JM Krueger: Sleep modifies glutamate decaarboxylase mRNA within the barrel cortex of rats after a mystacial whisker trim. *Sleep* 24, 261-266 (2000)

47. Mukhametov LM: Sleep in marine mammals. *Expt Brain Res* 8, 227-238 (1984)

48. Oleksenko AI, L.M. Mukhametov, I.G. Polyakova, A.Y. Supin & V.M. Kovalzon: Unihemispheric sleep deprivation in bottlenose dolphins. *J Sleep Res* 1, 40-44 (1992)

49. Werth E, P. Achermann & A.A. Borbély: Fronto-occipital EEG power gradients in human sleep. *J Sleep Res* 6, 102-112 (1997)

50. Drummond SPA, G.G. Brown, J.L. Stricker, R.B. Buxton, E.C. Wong & J.C. Gillin: Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *NeuroReport* 10, 3745-3748 (1999)

51. Maquet P: Functional neuroimaging of normal human sleep by positron emission tomography. *J Sleep Res* 9, 207-231 (2000)

52. Thomas M, H. Sing, G. Belenky, H. Holcomb, H. Mayberg, R. Dannals, H. Wagner, D. Thorne, K. Popp, L. Rowland, A. Welsh, S. Balwinski & D. Redmond: Neural basis of altertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 9, 335-352 (2000)

53. Mahowald M & C.H. Schenck: Dissociated state of wakefulness and sleep. *Neurology* 42, 44-52 (1992)

54. Pigarev IN, H.-C. Nothdurf & S. Kastner: Evidence for asynchronous development of sleep in cortical areas. *NeuroReport* 8, 2557-2560 (1997)

55. Jouvet M: The rhombencephalic phase of sleep. *Prog Brain Res* 1, 406-424 (1963)

56. Kristiansen K & G. Courtois: Rhythmic activity from isolated cerebral cortex EEG. *Clin Neurophysiol* 1, 265-272 (1949)

57. Kleitman N: Sleep and Wakefulness. The University of Chicago Press, Chicago (1963)

58. Jouvet M: Neurophysiology of the states of sleep. *Physiol Rev* 47, 117-177 (1967)

59. Kattler H, D.-J. Dijk & A.A. Borbély: Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *J Sleep Res* 3, 1599-1604 (1994)

60. Borbely AA: A two process model of sleep regulation. *Human Neurobiol* 1, 195-204 (1982)

61. Vyazovskiy V, A.A. Borbély & I. Tobler: Unilateral vibrissae stimulation during waking induces interhemispheric EEG asymmetry during subsequent sleep in the rat. *J Sleep Res* 9, 367-371 (2000)

62. Vyazovskiy V, A. Borbély & I. Tobler: Unilateral vibrissae stimulation induces interhemispheric EEG asymmetry during sleep in mice. *J Sleep Res* 11, 245 (2002)

63. Steriade M: Neuronal substrates for short-term plasticity during sleep oscillations in corticothalamic networks. In: The Regulation of Sleep. Eds Borbély A, Hayaushi O, Sejnowski T, Altman J. Human Frontier Science Program (2000)

64. Feinberg I, J.D. March, K. Flach, T. Maloney & J.D. March: Gamma distribution model describes maturational curves for delta wave amplitude, cortical metabolic rate and synaptic density. *J Eheor Biol* 142, 149-161 (1990)

65. Mascetti GG, M. Rugger & G. Vallortigara: Visual lateralization and monocular sleep in the domestic chick. *Cog Brain Res* 7, 451-463 (1999)

66. Walker MP, T. Brakefield, A. Morgan, J.A. Hobson & R. Stickgold: Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron* 35, 205-211 (2002)

67. Davis C, E.A. Kramar, J.W. Harding & J.W. Wright: Sleep deprivation abolishes maintenance of long-term potentiation in CA1. *Sleep* (Abst Supp) 25, A204-A205 (2002)

68. Guzman-Marin R, H. Gong, R. Szymusiak, D. McGinty: Sleep deprivation reduces proliferation of new cells in the rat hippocampus. *Sleep* (Abst Supp) 25, A108-A109 (2002)

Key Words: Plasticity, Brain Organization, Neuronal Group, Cytokine, Memory, Growth Factor, Neurotrophin, Sleep, Review

Send correspondence to: James M. Krueger, Ph.D. , Department of VCAPP, PO Box 646520, Pullman, WA 99164-6520, Tel:(509-335-8212, Fax: 509-335-4650, E-mail: Krueger@vetmed.wsu.edu