Published in final edited form as:
Curr Top Med Chem. 2011 September 1; 11(19): 2490–2492.

Local Use-Dependent Sleep; Synthesis of the New Paradigm

James M. Krueger[1,*] and **Giulio Tononi**[2]

[1]WWAMI Medical Education Program and the Sleep and Performance Research Center, Washington State University, Spokane WA 99210-1495, USA

[2]University of Wisconsin Madison, School of Medicine and Public Health, Department of Psychiatry, 6001 Research Park Blvd., Madison, WI 53719, USA

Abstract

The logic and potential mechanisms for a new paradigm, the local use-dependent view of sleep as a distributed dynamic process in brain, are presented. This new paradigm is needed because the current dominant top-down imposition of sleep on the brain by sleep regulatory centers is either silent or is of inadequate explanatory value for many well-known sleep phenomena, e.g. sleep inertia. Two mechanistic falsifiable hypotheses linking sleep to cell use and the emergence of sleep/wake states are presented. These hypotheses are not mutually exclusive and both firmly link sleep to activity-dependent epigenetic brain plasticity and the need to integrate and balance waking activity induced-network connectivity changes. The views presented herein emphasize the inseparability of sleep mechanisms from a connectivity sleep function.

INTRODUCTION

Exactly what is it that sleeps? This question is seldom addressed in part because sleep is considered a behavior; a static state; one is either asleep or not. Yet we know that an intact body or brain is not required for sleep to occur. There is no report in the literature of even a single case of complete absence of sleep in animal or human, despite millions of cases of brain lesions. This fact suggests that sleep is self-organizing and a fundamental property of any viable network of neurons and glia. Further, if in the intact animal we do not know the minimum tissue component necessary and sufficient for sleep to occur, it is difficult to speak of sleep regulation because we have yet to define what is regulated or where sleep is. Nevertheless, the current dominant paradigm in sleep research is one of sleep regulatory circuits imposing sleep on the brain [1]; this paradigm persists despite robust evidence that removal of any one of the sleep regulatory circuits (e.g. the anterior hypothalamus [2] or specific cell types within those circuits (e.g. basal forebrain cholinergic neurons [3, 4]) does not result in the absence of sleep.

Sleep is better viewed as a dynamic process, ever unfolding in terms of; a) mentation, b) degree of responsiveness to the environment, e.g. arousal thresholds, c) patterns of electrical activity or gene expression, and d) anatomical location of electrical or molecular changes. The dynamics of sleep are clearly dependent upon prior waking activity. Thus, arousal threshold (depth of sleep) is dependent on prior waking experience. Localized EEG delta power [5–7] or evoked response potentials [8], are dependent upon the intensity of specific local area activity during prior waking. The duration of sleep is dependent upon prior waking duration. Dream content is experience-dependent, being a function of what one

*Address correspondence to this author at the [1]WWAMI Medical Education Program and the Sleep and Performance Research Center, Washington State University, Spokane WA 99210-1495, USA; krueger@vetmed.wsu.edu; gtononi@wisc.edu.

knows and learned [9]. Further, the duration, type and architecture of sleep are dependent upon many internal dynamic variables including body temperature, hormone levels, water and caloric intake, and corresponding osmotic pressures and nutrient levels, circadian status, development stage, etc. Conversely, waking performance is dependent upon prior sleep duration [10, 11]. Further, sleep extends into wakefulness, e.g. sleep inertia.

Experimental models of sleep have heretofore been limited to whole animals. Mathematical modeling of sleep is largely focused on the 2-process model of sleep [12, 13] or flip-flop models that treat sleep as an on/off state [14]. These experimental and mathematical models need to be expanded to capture the dynamics of multiple influences on, and the local use-dependent characteristics, of sleep. For instance, the view that sleep is imposed upon the brain by sleep centers [15] is insufficient or silent on critical issues such as sleep inertia, dependency of waking performance on sleep, reorganization of sleep after brain injury, the nature of sleep homeostatic mechanisms, clinical conditions such as insomnia, and sleepiness and fatigue associated with multiple bodily ailments, such as rheumatoid arthritis and most autoimmune disorders, and with various chemotherapies. We [16, 17] and others [18–20] have proposed different views. These views treat sleep as a distributed process in brain. Thus, with the newer paradigm, parts of the brain can be asleep while other parts are awake, and local sleep states are use-dependent. With this newer paradigm it is easier to envision explanatory scenarios for the phenomena mentioned.

Neurons spontaneously form connections in brain and culture. Gene expression affects this process and alters functional properties of the network. Expression of certain genes, including many involved in connectivity, is activity-dependent [21, 22]. The activity-dependency of network connectivity-genes provides a bottom-up mechanism for targeting changes in the network to those synapses that were used. The use-dependent gene expression connectivity mechanism is not only an established epigenetic brain plasticity mechanism, but it is also a positive feedback loop since connectivity leads to re-use. The positive feedback of use and re-use would lead to a rigid non-plastic network[1] (see [16, 18] for the development of this argument). Negative feedback-damping mechanisms are needed to stabilize and preserve the use-dependent epigenetic plasticity. These negative feedback mechanisms lead to altered input-output relationships (state oscillations). Linking positive and negative feedback loops leads to oscillations in electrical signals and gene expression in such brain networks. At different phases of the oscillations, a given input leads to a different network output; the network can thus be considered in different states depending upon the oscillation phase. Synchronization of multiple network (e.g. cortical columns) state phase transitions emerges as sleep-wake cycling in whole animals.

The logic outlined above provides the framework to understand mechanisms that link cellular activity to sleep. Each of the authors has developed their own hypotheses concerning these mechanisms and both ideas are briefly presented here in recognition that they are not mutually exclusive and experimental verification and modification of each view is needed. Regardless, both views provide testable hypotheses and both lead to revolutionary concepts in sleep regulation.

The Krueger ATP-cytokine-adenosine mechanism is as follows [22, 23]: i) Neuro- and glio-transmission is associated with ATP release; ii) the consequent increase in extracellular ATP can thus be used to provide an index of prior local neuronal activity; iii) the ATP is detected by nearby glial purine type 2 receptors causing the release of sleep regulatory substances

[1]Embedded within our logic is the idea that sleep is a consequence of epigenetic plasticity and functions to serve it. Epigenetic plasticity has great evolutionary value; a value greater than the evolutionary costs of sleep. While asleep one does not reproduce, socialize, eat, or drink and one is subject to predation due to the reduced responsiveness to environmental cues.

(SRSs) such as tumor necrosis factor alpha (TNF), thereby translating prior neuronal activity into local levels of SRSs; iv) SRSs in turn, by a slow process (gene transcription/translation), alter electrical properties of nearby neurons by altering their own production and that of receptor populations, such as glutamate and adenosine receptors; v) The SRSs also, by a fast process (diffusion for short distances), directly interact with their receptors on neurons and alter electrical properties; vi) Further, ATP itself breaks down, releasing extracellular adenosine that in turn acts on adenosine purine type I receptors. These events are happening locally and the collective changes result in a shift in input-output relationships within the local neuronal/glia networks that originally exhibited the activity, i.e., a state shift.

The synaptic homeostasis hypothesis of sleep function [17, 24] also assumes that sleep has a use-dependent, local component, perhaps down to the cellular level [25, 26]. Given that sleep appears to be universal, pervasive, tightly regulated, and necessary [27], it likely serves a function that cannot be properly fulfilled when awake and interacting with the environment. According to the synaptic homeostasis hypothesis, sleep may be the price to pay for plasticity during wake. Briefly, in wake neurons need to adjust the strength of synapses to ensure that important signals can percolate through the brain and that patterns of activity selected by interactions with the environment are stored appropriately in the brain's connectivity matrix, which represents the sum total of its memory. It is likely that such a process occurs primarily by potentiating synapses strongly activated during behavior. However, the brain cannot afford a net increase in synaptic strength day after day, because of cellular costs in terms of energy, space, cellular supplies, such as proteins and membrane lipids, and saturation of signal-to-noise ratios. Sleep, then, would permit the renormalization of synaptic strength during an off-line period, when no new memories need to be laid down, and when the brain's connectivity matrix can be sampled through spontaneous activation in a way that is less biased by current activities. In mammals and birds, sleep slow waves may be instrumental in producing synaptic renormalization in a way that favors consolidation and the integration of new and old memories [28].

The manuscripts presented in this issue of Current Topics in Medicinal Chemistry fit nicely into our concepts and the more general idea of sleep as a distributed process, an emergent phenomenon from local events. These newer views have already led to new mathematical modeling of sleep [28, 29], new views of sleep pathologies [e.g. 30], and unique pharmacological approaches to sleep [23]. It seems that a paradigm shift is underway in sleep research.

Acknowledgments

This work was supported in part by NIH grant numbers NS025378 and NS031453 to JK and NIH Director's Pioneer Award (G.T.), NIH P20 MH077967 (G.T.), and NIH R01 NS055185 (G.T.) to GT.

References

1. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005; 437:1257–1263. [PubMed: 16251950]
2. Shoham S, Blatteis CM, Krueger JM. Effects of preoptic area lesions on muramyldipeptidenduced sleep and fever. Brain Res. 1989; 476:396–399. [PubMed: 2702477]
3. Kapás L, Obál F Jr, Book AA, Schweitzer JB, Wiley RG, Krueger JM. The effects of immunolesions of nerve growth factor-receptive neurons by 192 IgG-saporin on sleep. Brain Res. 1996; 712:53–59. [PubMed: 8705307]
4. Blanco-Centurion C, Xu M, Murillo-Rodriguez E, Gerashchenko D, Shiromani AM, Salin-pascual RJ, Hof PR, Shiromani PJ. Adenosine and sleep homeostasis in the basal forebrain. J Neurosci. 2006; 26:8092–8100. [PubMed: 16885223]

5. Kattler H, Dijk DJ, Borbély AA. Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. J Sleep Res. 1994; 3:159–164. [PubMed: 10607121]
6. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, Tononi G. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci. 2006; 9:1169–1176. [PubMed: 16936722]
7. Yasuda T, Yasuda K, Brown RA, Krueger JM. State-dependent effects of light-dark cycle on somatosensory and visual cortex EEG in rats. Am J Physiol. 2005; 289:R1083–R1089.
8. Rector DM, Topchiy IA, Carter KM, Rojas MJ. Local functional state differences between rat cortical columns. Brain Res. 2005; 1047:45–55. [PubMed: 15882842]
9. Nir Y, Tononi G. Dreaming and the brain: from phenomenology to neurophysiology. Trends Cogn Sci. 2010; 14:88–100. [PubMed: 20079677]
10. Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep. 2003; 26:117–126. [PubMed: 12683469]
11. Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. J Sleep Res. 2003; 12:1–12. [PubMed: 12603781]
12. Borbely AA. A two process model of sleep regulation. Human Neurobiol. 1982; 1:195–204.
13. McCauley P, Kalachev LV, Smith AD, Belenky G, Dinges DF, Van Dongen HPA. A new mathematical model for the homeostatic effects of sleep loss on neurobehavioral performance. J Theoretical Biol. 2009; 256:227–239.
14. Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. Nature. 2006; 441:589–594. [PubMed: 16688184]
15. Szymusiak R. Hypothalamic versus neocortical control of sleep. Curr Opin Pulmon Med. 2010; 16:530–535.
16. Krueger JM, Obál F. A neuronal group theory of sleep function. J Sleep Res. 1993; 2:63–69. [PubMed: 10607073]
17. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev. 2006; 10:49–62. [PubMed: 16376591]
18. Kavanau JL. Sleep and dynamic stabilization of neural circuitry: A review and synthesis. Behav Brain Res. 1994; 63:111–126. [PubMed: 7999294]
19. Benington J, Heller HC. Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol. 1995; 45:347–360. [PubMed: 7624482]
20. Mahowald MW, Schenck CH. Dissociated states of wakefulness and sleep. Neurology. 1992; 42:44–51. [PubMed: 1630638]
21. Brandt J, Churchill L, Guan Z, Fang J, Chen L, Krueger JM. Sleep deprivation, but not a whisker trim, increases nerve growth factor within barrel cortical neurons. Brain Res. 2001; 898:105–112. [PubMed: 11292453]
22. Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J. Sleep as a fundamental property of neuronal assemblies. Nat Rev Neurosci. 2008; 9:910–919. [PubMed: 18985047]
23. Krueger JM, Taishi P, De A, Davis C, Winters BD, Clinton J, Szentirmai E, Zielinski MR. ATP and the purine type 2 X7 receptor affect sleep. J App Physiol. 2010; 109:1318–1327.
24. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull. 2003; 62:143–150. [PubMed: 14638388]
25. Tononi G. What is the minimal brain unit capable of sleep? World Federation Sleep. Res Soc Newslett. 1996; 5:9–11.
26. Borbély AA, Tononi G. The quest for the essence of sleep. Daedalus. 1998; 127:167–196.
27. Cirelli C, Tononi G. Is sleep essential? PLoS Biol. 2008; 6:e216. [PubMed: 18752355]
28. Olcese U, Esser SK, Tononi G. Sleep and synaptic renormalization: A computational study. J Neurophysiol. 2010; 104(6):3476–3493. [PubMed: 20926617]
29. Roy S, Krueger JM, Rector DM, Wan Y. A network model for activity-dependent sleep regulation. J Theoretical Biol. 2008; 253:462–468.

30. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry. 2004; 161:2126–2128. [PubMed: 15514418]