COMMENTARY

Unihemispheric Sleep: An Enigma for Current Models of Sleep-Wake Regulation

Commentary on Lyamin et al. Monoamine release during unihemispheric sleep and unihemispheric waking in the fur seal. *SLEEP* 2016;39(3):625–636.

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Some mammals (whales, dolphins, fur seals, sea lions) sleep with one hemisphere of the brain being asleep while the other is awake.[1,2] This is referred to as unihemispheric slow wave sleep (USWS) and contrasts with the bihemispheric slow-wave sleep (BSWS) exhibited by humans and other mammals. Whales (*Delphinapterus leucas*) and dolphins (*Tursiops truncates*) show only USWS.[3,4] Northern fur seals and sea lions (family Otariidae) are aquatic and terrestrial. While in water these animals have USWS, like cetaceans, but on land they have both USWS and BSWS.[3] It is unclear whether cetaceans have REM sleep, whereas Otariidae have REM sleep on land, and it is always bilateral. Some birds also have USWS,[5,6] but neurochemicals related to USWS have only been measured in the fur seal. The evolutionary basis of USWS is unclear.[7,8]

Polysomnography studies have conclusively shown that USWS is indeed sleep because one hemisphere has high-amplitude slow wave activity (1.2–4 Hz), while the other hemisphere has desynchronized EEG activity.[5,6,9] The daily quota of sleep is equally distributed between the hemispheres.[10] If the hemisphere with USWS is repeatedly interrupted, then that hemisphere will have rebound USWS indicating a homeostatic need for USWS in that hemisphere.[5,6,9] In such unihemispheric sleep deprivation studies, there is no compensatory increase in sleep in the non-deprived hemisphere, indicating that the homeostatic need for sleep accumulates independently in each hemisphere. These data indicate that USWS is actively generated and there is a compensatory need for it.

The discovery of unihemispheric sleep is a boon to sleep research as it provides a unique opportunity to empirically test neural circuit models of sleep-wake regulation. Lyamin, Mukhametov, Siegel and colleagues have clearly recognized this and have conducted elegant studies in northern fur seals (*Callorthinus ursinus*) to test the hypothesis that neurochemicals linked to wakefulness are elevated in the awake hemisphere compared to the hemisphere with USWS.[11–13] In these studies the seals were instrumented to record the EEG, EMG, and EOG, and also implanted with pairs of guide cannulas targeted in symmetrical positions in each hemisphere. Microdialysis probes collected extracellular fluid from each site every 10 minutes and the levels of acetylcholine, histamine, norepinephrine (NE), and serotonin in the sample were assessed. The seals were maintained on a 12–12h light-dark cycle and samples were collected in active waking, quiet waking, BSWS, USWS, and REM sleep. Acetylcholine was measured in the first study,[12] serotonin in the second study,[11] and in a study published in the current issue of *SLEEP*, Lyamin and colleagues[13] measured levels of histamine, norepinephrine, and serotonin.

They found that cortical levels of histamine, NE, and serotonin were highest during active waking, declined in BSWS, and were lowest in REM sleep. Subcortical levels of NE (hypothalamus) and serotonin (caudate and thalamus) showed a pattern similar to that seen in the cortex. In their previous study they had found that acetylcholine levels were maximal during active wake, declined during quiet waking and REM sleep, and were minimal in BSWS.[12] Thus, in BSWS, the levels of these neurochemicals are consistent with the pattern seen in other terrestrial mammals and correlates very well with the pattern of activity of their respective neurons (Table 1).

The surprise was that during USWS levels of histamine, NE, and serotonin were not higher in the desynchronized (awake) hemisphere compared to the contralateral hemisphere with USWS.[13] On the other hand, acetylcholine release in the cortex was lateralized and tightly linked to the hemisphere that was awake.[12] Therefore, the current circuit models cannot explain how activity of histamine, NE, and serotonin neurons drives cortical waking in one hemisphere and not in the other. These models also fail to explain accumulation of sleep drive in one hemisphere and not the other.

We agree that more data are needed. For instance, the next step would be to measure orexin levels in the USWS model system since orexin neurons are active in waking but silent in REM sleep.[14,15] However, it is possible that orexin may also not be lateralized to the awake hemisphere since orexin levels are minimal in humans with an activated EEG during pain.[16] Moreover, neurochemicals associated with sleep, such as GABA and melanin concentrating hormone (MCH) should be measured.[17,18] It is important to measure GABA since it is strongly linked to sleep. Moreover, new data in mice (who only have BSWS) indicate that histamine neurons also release GABA.[19] Is GABA lateralized in USWS? Peptides associated with activity, such as prokineticin[20] and neuropeptide S[21] should also be measured. Moreover, the effects of sleep deprivation in the USWS model on levels of neurotransmitters and peptides should also be assessed.

The current widely accepted circuit model of sleep-wake regulation is based on studies in animals with BSWS.[22] The underlying premise of this model is that separate populations of neurons are responsible for wakefulness, slow wave sleep, and REM sleep (summarized in Table 1 and Figure 1A). Although stimulation of specific phenotypes of neurons can robustly influence state[17,23] lesions (genetic or neurotoxin) of one or multiple arousal populations does not change daily levels of sleep.[24] Moreover, areas of the cortex can be "offline" during waking in humans and rats, suggesting that parts of the brain

Table 1—Summary of changes in neuronal activity and neurotransmitters in wake, BSWS, USWS, and REM sleep.

	Neuronal Discharge[a]			Release (Cx-CSF)[b] Terrestrial Mammals (primates, cats, rats)			Bilateral Release Fur Seals (on land)			Unihemisphere Fur Seals			
							Bilateral SWS			Unihemisphere Sleep			
Neurotransmitters	**W**	**S**	**RS**	**W**	**S**	**RS**	**W**	**S**	**RS**	**BW**	**UW**	**USWS**	**References**
Wake promoting													
Acetylcholine	+++	+	+++	+++	+	+++	+++	+	+++	+++	+++	+	12, 38, 39
Histamine	+++	+	0	+++	+		+++	+	+	+++	+	+	13, 40
Norepinephrine	+++	+	0	+++	+		+++	+	+	+++	+	+	13, 41, 42
Orexin	+++	+	0	+++	+								14, 15, 18, 43
Serotonin	+++	+	0	+++	+		++	+	+	+++	+	+	11, 44, 45
Sleep promoting													
GABA / Galanin (PO)	0	++	+++	c									46–50
MCH	0	++	+++	+	+++								14, 17, 18

Desynchronized EEG is produced both in wake and REM sleep. Blank boxes indicate work that needs to be done. [a] Neuronal discharge represents activity relative to wake. 0 = little or no neuronal activity. [b] Neurotransmitter levels are relative to wake. [c] GABA has been measured in the posterior hypothalamus and pons but needs to be measured in cortex in association with USWS. W, wake; S, slow-wave sleep; RS, REM sleep; BW, bilateral wake; UW, unilateral wake; USWS, unihemispheric slow-wave sleep; MCH, melanin concentrating hormone; PO, preoptic area; Cx, cortex; CSF, cerebrospinal fluid; SWS, slow-wave sleep.

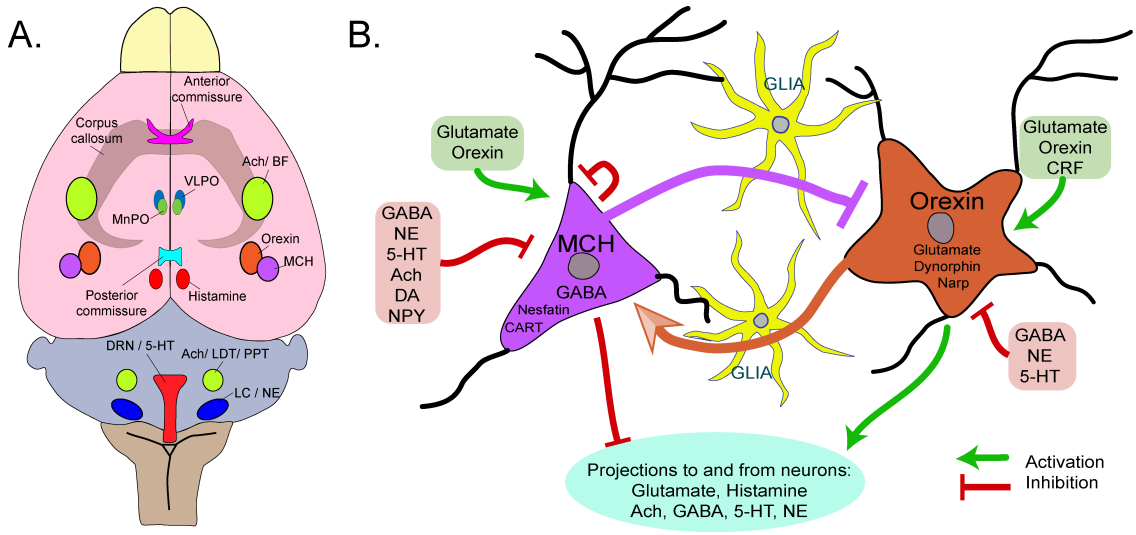

Figure 1—(A) Horizontal view of the rat brain depicts the regional location of neurons implicated in regulating wake and slow wave sleep (SWS). Neurons regulating REM sleep are located in the brainstem and not depicted here since REM sleep only occurs in both hemispheres. All of these neurons innervate cortical and subcortical regions and release their respective neurotransmitters onto downstream targets. The serotonin neurons are located in the midline, while the other neurotransmitter/peptide containing neurons are located laterally. The extent to which these neurons crossover to the contralateral hemisphere in animals with USWS is not known, and analysis of the decussation pathways (corpus callosum, anterior commissure, and posterior commissure) are inconclusive.[36,37] **(B)** Schematic illustration that local interactions between glia and neurons change local excitability. Wake-induced adenosine released from glia dampens excitability of the wake-active neurons (orexin), which diminishes local wake drive. This small network is affected by local levels of glucose. This network is based upon the local use dependent model.[32] Abbreviations: ventrolateral preoptic nucleus (VLPO); median preoptic nucleus (MnPO); basal forebrain (BF); dorsal raphe nucleus (DRN); laterodorsal tegmental nucleus (LDT); posterior pretectal nucleus (PPT); Locus ceruleus (LC); Melanin concentrating hormone (MCH) γ-aminobutyric acid (GABA); norepinephrine (NE); serotonin (5-HT); acetylcholine (Ach); dopamine (DA); neuropeptide Y (NPY); corticotropin releasing factor (CRF); cocaine-amphetamine-regulated transcript (CART); neuronal activity regulated pentraxin (Narp).

can be asleep even in waking.[25,26] Other data indicate that activating local neurons in the barrel cortex produces a homeostatic load at that site, which is then dissipated by increased sleep at the site.[27] Thus, sleep may represent a collective output of small networks of neurons and sleep homeostasis is a reflection of local use.[28] This is in contrast with the currently accepted model that sleep and wake result from activity of phenotype-specific subcortical neurons.[22]

In the small network model, glia are included (see Figure 1B).[28] Glia outnumber neurons in the brain and a growing body of evidence now considers glia to be partners with neurons in regulating sleep.[29] Emergent sleep-like states are evident in small neuronal-glial networks grown in vitro.[30] In wildtype C57BL/6J mice optogenetic activation of local astrocytes in the posterior hypothalamus increases sleep.[31] Gliotransmitters such as adenosine likely impart the homeostatic load locally.[29] This supports the idea of "local use dependent sleep."[32] The interaction between glia and neurons in small networks efficiently regulates synaptic strength.[33,34] The local use dependent model nicely explains the accumulation of sleep

in one hemisphere and not in the other in response to USWS deprivation.

We are grateful to Lyamin and colleagues for pursuing very difficult studies to identify the cellular correlates of USWS and BSWS in *Otariidae*. We recognize that research in other animal models will expedite discovery. We suggest harnessing the power of genetics to identify unihemispheric sleep in roundworms (*C. elegans*), fruit flies (*D. melanogoster*), and zebrafish (*D. danio*). For instance, in these model systems developmental cell fate mapping approach could target cells in one hemisphere and not the other.[35] We also suggest the use of new methods such as optogenetics and pharmacogenetics in birds. Because the size of the bird brain is small, it could be probed by new tissue clearing methods such as CLARITY to identify difference in connectivity between hemispheres and comparisons can be made with the mouse brain. We believe that a collective effort is necessary to identify the cellular basis of sleep.

CITATION

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