CHAPTER 5

Evoked Electrophysiological and Vascular Responses across Sleep

David M. Rector
Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology, Washington State University

INTRODUCTION

Sleep is traditionally defined by a collection of metrics assessed in concert to determine an organism's state. These include posture, EEG waveforms, cardio-respiratory rate, eye movement, and muscle tone, to name a few. However, sleep state characteristics are often difficult to interpret during abnormal sleep and under conditions of sleep pathology because those processes that normally produce the standard metrics are disturbed in various ways. For example, during total sleep deprivation, delta wave intrusions are present during periods that otherwise appear as waking, and may define a putative "microsleep" state (e.g., Grenèche et al., 2008). Microsleep may represent brief sleep periods and encompass processes similar to sleep. Leg movements during restless-leg syndrome occur during sleep, in spite of the fact that muscles are supposed to be relaxed. Mahowald and Schenck (2005) propose that individuals with parasomnias, such as sleepwalking, are simultaneously awake and asleep. Such conditions make sleep difficult to study because the normal collection of metrics is not present.

Traditional sleep characteristics may also represent only those mechanisms that have developed under niche appropriate conditions. Specifically, normal conditions dictate that an organism maximize the amount of sleep it acquires during times when other functions such as foraging and reproduction may not be optimal. Since sleep is a highly vulnerable state for most animals, it must occur at specific times when food is not available and be undisturbed by predators. Humans, however, have changed these rules with the need to be productive 24 hours a day, 7 days a week, and 356 days a year (Balkin et al., 2004). The new rules have produced conditions where we fail to get enough sleep, resulting in a number of pathologies such as increased sleep-loss related accidents, insomnia, daytime sleepiness, obstructive sleep apnea, diabetes, heart failure, depression, and

Sleep and Brain Activity
DOI: http://dx.doi.org/10.1016/B978-0-12-384995-3.00005-8

many other illnesses that may have their origins in, or be exacerbated by sleep loss (Grandner et al., 2010).

Additionally, sleep is not necessarily a whole brain phenomenon (Krueger and Obal, 1993; Kavanau, 1996; Pigarev et al., 1997; Krueger et al., 2008). An increasing number of studies show aspects similar to sleep and wake can occur simultaneously or at different levels in different brain regions. First demonstrated in humans by stimulating one hand more than another (Kattler et al., 1994), this is particularly evident in rodents that use their whiskers in the dark, and visual system during the light; they exhibit greater amounts of slow wave activity in the respective brain regions that are used more (Yasuda et al., 2005). Many other examples have followed in both humans and animals (e.g., Huber et al., 2006). In principle, if sleep is restorative, then any region that is used more should exhibit characteristics of sleep more often than other regions. With this perspective in mind, traditional sleep markers may be inadequate to define sleep, especially under abnormal conditions. Thus, the development of new sleep markers is needed. Ideally, these markers should be more closely related to those processes involved in controlling sleep.

There are at least two main issues that must be addressed in the next phases of sleep research. First, as we begin to understand the cellular and physiological consequences of sleep, we must identify better markers of sleep state and need. Second, given that humans will increasingly be driven to deprive themselves of sleep, we may identify additional long and short term consequences to sleep loss that have not yet been appreciated. More specifically, people who are driven to increase productivity are frequently frustrated by sleepiness, and use many physical and pharmacological mechanisms to stay awake (Wesensten et al., 2004). While they may experience short term gains in productivity (Van Dongen et al., 2003), detrimental long term consequences could build up over time.

Our studies have started to address these issues from several different perspectives. Evoked electrical and hemodynamic markers are predictive of sleep states, and in some ways may be better than traditional measures since they can be localized to specific brain regions experiencing differential use, and on average, correlate with whole animal state. We have also investigated the relationship between vascular compliance and sleep, leading to a sleep control theory that may help to integrate many long standing ideas of energy restoration and recent discoveries involving ATP, cytokines, and sleep, with the potential for severe long term consequences if energy restoration is not permitted during forced extended waking.

ELECTRICAL MARKERS OF SLEEP AND SLEEPINESS

Traditional electrical sleep state markers have focused on passive EEG measurements, which categorize the amount of power in different frequency bands. Since the EEG is principally derived from synchronous tissue activity, much research has investigated the source of oscillations at the various frequencies. However, due to the electrical diffusion in skin and scalp, EEG signals tend to be an average over large regions. The introduction of high density EEG (e.g., Massimini et al., 2009) and mathematical source localization algorithms to reduce the bulk averaging of the electrical signals has shown that such EEG characteristics are indeed not observed globally across the brain, but rather have greater power in those areas that have been used more during waking.

However, the passive measurement of tissue activity synchronization may not be enough to detect subtle changes in tissue state. Especially since similar synchronized activity can be observed under a mixture of different states. Observations beginning many years ago probed tissue state by stimulating it with specific input, then related differential electrical evoked responses across different sleep states (for review see Colrain and Campbell, 2007). Indeed, the electrical excitability of the cortex is inherently dependent on many factors including sleep state as well as arousal level and attention, which all may be inherently related to those processes that regulate sleep.

A Focus on Cortical Columns

One major hurdle when investigating regional sleep is the difficulty in defining the least significant component that can sleep. Since evidence is rapidly building that something less than the whole brain can be asleep at any given moment in time, how far do we have to probe to find the smallest component that sleeps? If sleep is defined as simple rest/activity cycles, then single cells may sleep. However, since cells within cortical columns are more highly interconnected than between columns (Shaw et al., 1982), the cortical column may represent a functional processing unit in the cortex (Koch, 2004). Additionally, vessels within microcapillary beds appear to be regulated at the cortical column level (Fehm et al., 2006). Thus, for a number of practical reasons, including ease of cortical surface access, our investigations to date have focused on markers that originate from surface cortical columns.

Methods of Recording Electrical Markers

Previous electrical measures to assess sleep typically use passive measures. By recording and calculating the frequency content of EEG, EOG, EKG, and

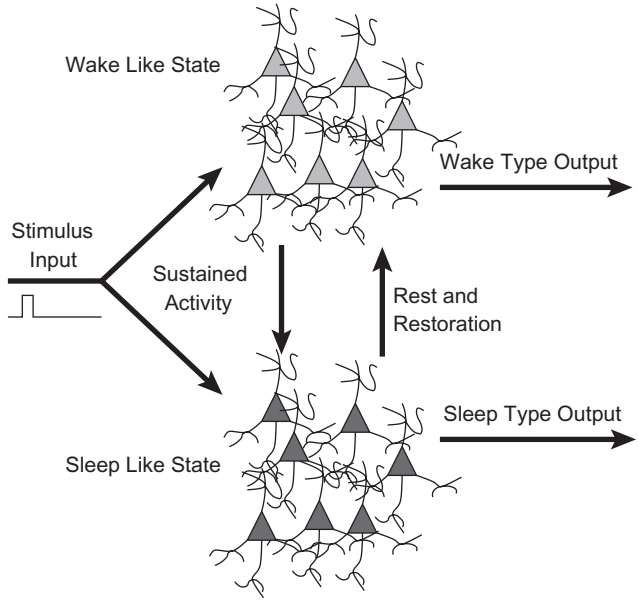

Figure 5.1 As a starting point in our studies, we consider the cortical column to be an operational unit of tightly interconnected cells within the brain for functional purposes (see text). Additionally, microcapillary beds are arranged such that key regulatory points serve individual columns and are sensitive to activity within the cortical column. When a cortical column receives a stimulus input, it produces an output response. The electrical consequences of the response can be detected as a surface evoked response potential because most of the cells act together creating a large electrical field, recorded with a cortical surface electrode or EEG electrode. Microvessel dilation is also triggered by enhanced electrical activity, generating an evoked hemodynamic response. Given identical input characteristics, the output response will be different depending on whether the column is in its wake-like or sleep-like state. The differential responses provide a marker for state that can be probed with the input stimulus, as long as the stimulus does not change the animal's state.

EMG, sleep can generally be inferred from stereotypical patterns. As mentioned earlier, these patterns break down under abnormal sleep or in the context of sleep pathologies, thus new measures are needed. We have focused on using active measures to probe sleep states that presume that the input/output relationships of the cortex will be different during different states (Fig. 5.1).

To record electrical evoked responses from cortical columns, we have used several approaches. First, the differences across cortical columns can be mapped using high density electrode arrays placed on the cortical surface to record the electrocorticogram (ECoG). By stimulating specific sensory modalities, then identifying the particular electrode that produces the

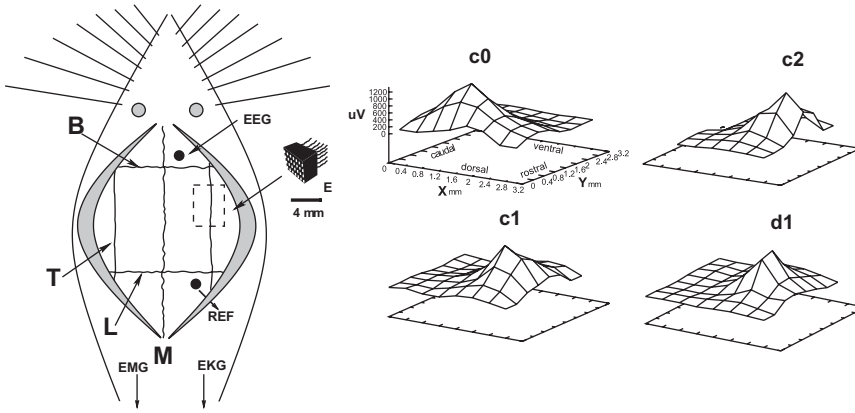

Figure 5.2 We placed cortical surface electrode arrays over the somatosensory cortex of the rat and recorded the two-dimensional pattern of electrical activity after stimulation. The 64-channel electrode array was used to map field potentials on the somatosensory cortical surface while the rat's whiskers were stimulated. Screw electrodes were used for recording frontal and parietal EEG. Stainless steel wire was threaded across the rib cage to record EKG and inserted into the neck muscles to record EMG. Several anchor screws were placed around the skull for additional headstage support. For some rats, two pairs of stainless steel screw electrodes were placed 4 mm apart over the somatosensory cortex on the temporal ridge (T), 1 mm caudal to bregma (B). The 64 channel electrode array was constructed from black Delrin and 0.2 mm stainless steel wires spaced 0.4 mm apart. A squared opening in the skull over the somatosensory cortex, outlined by the dotted line, allowed placement of the array on the cortical surface (E). One screw electrode was placed rostral to bregma near the midline (M) for frontal lobe EEG and one was placed near lambda (L) for ground reference (REF). The location of each whisker barrel was mapped by twitching whiskers in sequence while generating 2D surface maps of electrical potentials through the electrode array. To illustrate, twitching whiskers c0, c1, c2, and d1 each produced unique maps (right panels) with the initial peak amplitude corresponding to the location of the whisker barrel associated with that whisker. Subsequent analysis used the electrode within the array that corresponded to the location closest to the cortical column for the stimulated whisker.

earliest and largest response, a surface electrode array can be used to associate particular electrodes with a given cortical column (Fig. 5.2). Second, the mapping procedure is not always required since specific stimuli will necessarily activate a particular cortical column, and the earliest components of an evoked response recorded with an EEG electrode will correspond to a specific location (Penfield, 1958). Either way, electrical evoked responses triggered by stimulus events can be associated with activation of specific cortical regions, and used to assess the state of that region. We have used both somatosensory stimulation in rats through whisker stimulation and auditory stimulation through speaker clicks to elicit evoked responses.

Since low level stimuli do not elicit arousal (Phillips et al., 2011a), they can be used to probe cortical state during sleep.

State Dependent Electrical Evoked Responses

The amplitude and latency of the electrical evoked response from any sensory modality has been clearly linked to different conscious states beginning with Weitzman and Kremen (1965). Specifically, when using low level stimuli, evoked responses are significantly larger on average during sleep than during wake and REM sleep (Rector et al., 2005). Since the same stimulus (input) produces a different evoked response (output) dependent on sleep state, we postulate that evoked response characteristics can be used as a marker for state, at least within individual cortical columns. Furthermore, if we imagine with Sherrington that each cortical column can be represented by a light (Sherrington, 1951), "on" when active and "off" when quiescent, then the brain could be seen as a constellation of twinkling lights, usually "on" when awake, and usually "off" when asleep, but with the possibility to flip on or off depending on the need for attention or sleep, respectively (Roy et al., 2008). Many studies on attention and arousal control circuits provide a basis for turning the cortical columns "on" (Saper et al., 2001), and most likely they are configured to keep most of the brain awake during critical periods when the organism requires maximum alertness. Central control circuits may exist specifically to maintain an animal's vigilance during those periods when it is most efficient to do so. However, when pushed into abnormal conditions (e.g., trauma or extended waking), those processes that drive the columns to turn "off" and enter their sleep-like state may compete with arousal mechanisms, increasing the likelihood that a given column may enter the sleep-like state while the whole animal is awake. In the following sections, we will postulate that a lack of resources could potentially be at the root of this drive. Further investigations into the mechanisms that produce the state dependent input/output relationships will provide tremendous insight into those processes that regulate sleep.

Slow Waves, Cortical Column Cell Membrane Potential, and Evoked Responses

Initial studies into the mechanisms that underlie the state dependent evoked response characteristics suggest that baseline membrane potential is a principal component. We hypothesize that cells are depolarized during the active, wake-like state, and hyperpolarized during the quiescent,

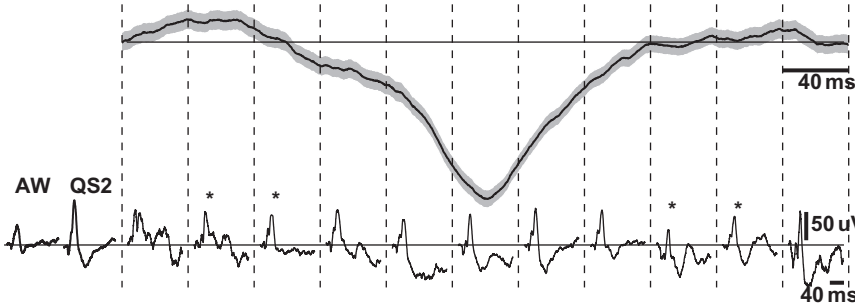

Figure 5.3 During quiet sleep periods with high amplitude slow waves, we filtered the EEG between 0 and 4 Hz, then identified the time point for each nadir in the slow waves. By registering the nadir of each slow wave in time, we created an average slow wave trace (top trace). The gray region around the average slow wave represents the standard error of the mean for each sample point. For each stimulus, the evoked response was averaged based on its timing relative to the nearest nadir in 40 ms bins. Evoked responses that occurred 80 ms before or after the nadir were significantly larger (*, $p < 0.1$) than responses that occurred 120 to 160 ms before or after the nadir. Evoked response traces below the average slow wave represent average data from one animal with the average active wake (AW) and quiet sleep (QS2) ERP traces plotted on the left for comparison to the typical state-related responses.

sleep-like state. Evoked responses have lower latency and are lower amplitude during the wake-like depolarized state because synaptic activation can occur more rapidly when the membrane potential is depolarized, and the change in membrane potential is smaller, resulting in a smaller averaged evoked response. Evoked responses have longer latency and are larger in amplitude in the hyperpolarized, sleep-like state because it takes more time to activate the synapses from a lower membrane potential. When activated, the total change in membrane potential is larger, starting from a lower initial value, resulting in a larger evoked response.

Many experiments on anesthetized animals (Steriade et al., 1993; Timofeev et al., 1996) and later in waking and sleeping animals (Steriade et al., 2001), support the hypothesis stated above. Delta slow waves, which are characteristic of sleep, result from the rhythmic alteration of membrane potential between the depolarized and hyperpolarized states. Work by Massimini et al. (2003) and ourselves (Rector et al., 2009a) show that evoked responses generated during the up (depolarized) state of slow wave sleep are remarkably similar to those generated during waking, while evoked potentials generated during the down (hyperpolarized) state are similar to those during sleep (Fig. 5.3). Further analysis on individual evoked responses demonstrates that roughly half the evoked responses during slow

wave sleep are much larger than the average responses observed during sleep, while the other half are small and wake-like, as would be expected from a roughly 50% duty cycle within the slow wave rhythm (Rector et al., 2009a). When averaged across the entire record, the evoked responses during sleep appear larger than during wake because the sleep-like responses are more than twice the amplitude of the wake-like responses.

Several key implications of the state dependent evoked responses are important to consider. First, the results imply that a relative measure of average baseline membrane potential of cells within a cortical column can be inferred from the size and latency of the evoked response. This is a remarkable possibility considering that the measurement can be noninvasive from the scalp surface. Second, stimuli should be low amplitude, and should not arouse the animal statistically more often than without the stimuli (Phillips et al., 2011a). However, if animals do wake up during our stimulus protocol, they tend to wake up from stimuli presented during the up states of slow wave sleep, corresponding to the low amplitude evoked response, but not when presented during the down state (Phillips et al., 2011a). This indicates that additional sensory integration and processing is possible during sleep, but only when the cells are in the depolarized (wake-like or up) state.

Lack of Cortical Gain Control during Sleep

Our more recent experiments delve even deeper into the state dependent input/output relationships and show additional important features. Stimuli presented during wake and REM sleep produce modulated evoked responses as would be expected by typical stimulus/response curves. However, during sleep, the evoked responses are constant amplitude, regardless of stimulus intensity (Fig. 5.4). These results suggest that when the cells within the column are in their hyperpolarized or down state, they are not able to adequately reflect the stimulus intensity. Since the evoked response amplitude is constant, regardless of stimulus intensity, it appears that the down/hyperpolarized state of the cortical column does not provide input gain control (Phillips et al., 2011b).

Other Considerations

There is much work remaining to support the notion that evoked response characteristics represent "wake-like" and "sleep-like" states, especially during slow wave sleep. Up and down states during slow wave sleep might be physiologically different from the fluctuations between silent and desynchronized states characteristic of waking. Indeed the cholinergic

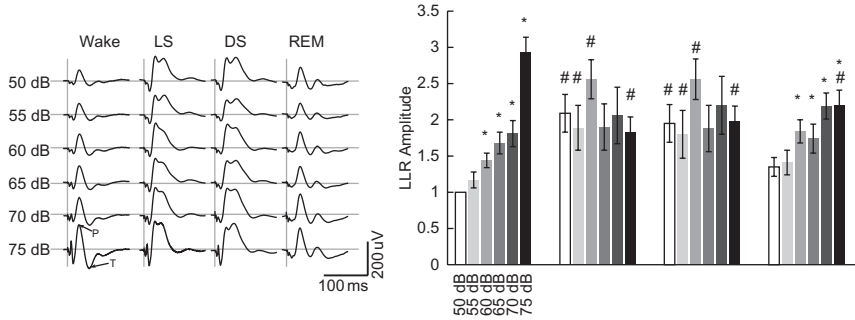

Figure 5.4 Example electrical evoked response traces beginning 150 ms after the stimulus from one animal show the state and stimulus intensity changes in the cortical response to auditory stimulation. The amplitudes increased consistently with increased stimulation intensity during Wake and rapid eye movement sleep (REM), but were at a constant level during light sleep (LS) and deep sleep (DS). We also observed a significantly longer trough latency during LS and DS due to the presence of a second waveform that extended the duration of the response. The average response amplitudes for all animals across state and stimulus intensity were divided by the average 50 dB wake value in order to normalize values across animal and plotted in bar graph form on the right. During Wake and rapid eye movement sleep (REM), increased stimulation intensity elicited larger amplitude components. No significant changes in amplitude were seen during light sleep (LS) or deep sleep (DS). This result caused the low level stimuli (50 to 60 dB) to appear larger during LS and DS than Wake, and high level stimuli (70 to 75 dB) to appear smaller. During rapid eye movement sleep (REM), the response at the highest stimulus intensity was significantly lower when compared to the Wake value. Significant differences across stimulation intensity compared to the 50 dB level within a state are marked with a (*), $p < 0.05$ Mann-Whitney U test. Significant differences across state compared to Wake at the same intensity level are marked with a (#).

inputs are different, and connectivity between distant columns is also reduced, perhaps related to inhibition of arousal systems (Szymusiak and McGinty, 2008). Finally, the thalamocortical circuit is most certainly synchronizing if not orchestrating these fluctuations within the intact preparation. While the up state during slow wave sleep is not necessarily identical to the waking state, there is much striking evidence to support the notion that the up state during slow wave sleep and the waking state share many physiological and functional similarities. Fundamentally, this relationship will help us eventually understand performance deficits during sleep deprivation, and other issues found in many sleep pathologies. Since hyperpolarized cells exhibit lower metabolism and energy demands, it is possible that this state may be related to the restorative aspects of sleep (Benington and Heller, 1995). In the next section, we investigate a vascular sleep state marker with direct ties to the membrane potential changes.

EVOKED VASCULAR AND HEMODYNAMIC RELATIONSHIPS TO SLEEP

With cholinergic activating/arousal systems driving cells into their depolarized/up state, we do not yet have a mechanism for driving cells into a sleep-like state. Many studies have shown that overall brain metabolism is lower during quiet sleep compared to waking and REM (Braun et al., 1997). This makes sense since cortical activity is lower during sleep. Thus, if sleep is a restorative process, then energy stores need to be replenished at a rate faster than they are used during sleep. Since metabolic requirements of the depolarized/up state are higher due to a large amount of spontaneous activity (Steriade et al., 2001; Vyazovskiy et al., 2009), it is possible that a reduction in metabolite reserves, including oxygen and sugar, makes it difficult for the cells to maintain a depolarized membrane potential, and recovery occurs during the hyperpolarized/down state. Additionally, blood perfusion limits may reduce the amount of heat that can be removed from active tissue, further compromising cellular function (Lydig, 1987; McGinty and Szymusiak, 1990). To test this hypothesis, we used pulse oximetry to record changes in oxy- and deoxyhemoglobin concentration during evoked responses across sleep and waking.

Evoked Hemodynamic Responses

Locally regulated neurovascular coupling increases blood volume and flow to active brain tissue for just-in-time metabolite delivery and waste removal (Roy and Sherrington, 1890; Filosa and Blanco, 2007; Buxton et al., 2004). Conditions of impaired perfusion and overdriven cells underlie significant injury described for pathological conditions including stroke, epilepsy, head trauma, and obstructive sleep apnea (Macey et al., 2008). Yet everyday activities, such as extended time spent on a task and mild sleep deprivation, cause cognitive and performance deficits. Fundamental limitations in vascular compliance may extend beyond pathological conditions and provide a unified model in which cells are routinely exposed to limited perfusion, with consequences to performance, and must hyperpolarize for recovery (Fig. 5.5).

While compliance is a factor in recent Windkessel models of vascular dynamics (Huppert et al., 2007), saturation of blood delivery is only considered under extreme conditions such as epilepsy. However, that notion developed from animals under anesthesia or sedation (Devor et al., 2003), conditions characterized by vascular dilation and significantly lower metabolism.

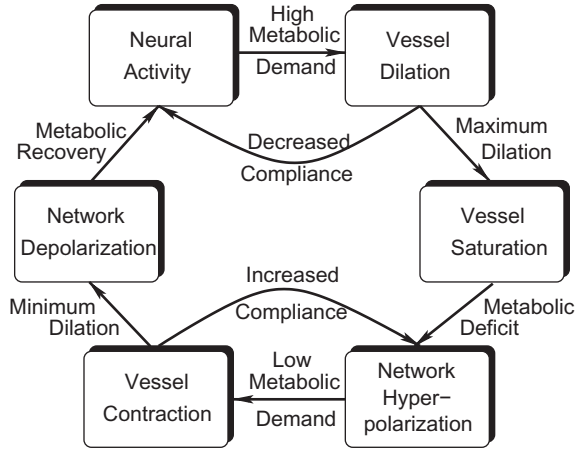

Figure 5.5 Our model of vascular regulation across wake and sleep-like states suggests physical limits in the ability of blood to deliver metabolites to tissue may underlie state transitions. Neural activity demands metabolites, initiating vasodilation through many well-known neural and chemical mechanisms. High metabolic demand associated with sustained activity will gradually decrease vessel compliance, limiting the ability to deliver oxygen and glucose. When vessels reach saturation, the potential for metabolic deficit may trigger a protective mechanism such that the network hyperpolarizes (down, sleep-like state) with lower metabolic demand, and restoration of vessel compliance. After sufficient recovery, the tissue can depolarize, entering its up (wake-like) state. This general model goes beyond pathological conditions and predicts everyday performance limits.

During normal waking, vascular smooth muscle compliance and expansion under prolonged neural activity may be limited by tissue compression (Schei et al., 2009; Rector et al., 2009b; Behzadi and Liu, 2005). Thus, physical vascular limits to deliver blood and remove waste products within local activated brain regions may ultimately restrict the normal period over which brain cells can operate and will impose functional consequences in that region. This hypothesis challenges conventional notions about the limits of vascular compliance and provides a comprehensive, unified physiological explanation for cognitive and performance deficits resulting from extended use of neuronal pathways, time-on-task effects, and sleep deprivation. In theory, if the resources required for optimal and sustained performance were understood, we might be able to devise methods to counteract the consequences of neural activity and sleep loss, and increase sustained activity periods. However, neural tissue is confined within the skull, and ultimately limited by hydrodynamic forces, vascular expansion, nutrient delivery, and heat removal. If these limits are exceeded over the long term, cellular trauma could result.

Methods to Record Evoked Vascular Responses

Most hemodynamic studies during sleep used global cerebral blood flow measures (e.g., Braun et al., 1997), or other slow measures of localized blood volume changes such as fMRI BOLD or PET imaging methods. We implanted LEDs and photodiodes into animals to obtain continuous spectroscopic measurements of oxy- and deoxyhemoglobin concentrations, similar to pulse oximetry. Using this technique, evoked changes in hemoglobin concentration can be assessed continuously at greater than 1000 samples per second, providing high resolution measurements of oxy- and deoxyhemoglobin concentration during sleep/wake cycles and concomitant with evoked response.

Evoked Hemodynamic Changes across State

Our initial recordings revealed that the evoked hemodynamic response was much larger during sleep than during wake (Fig. 5.6). Initially we assumed this was due to the larger evoked electrical response or due to increased synchronized activity, however, the increase was many times larger than the corresponding evoked electrical signal. This result, combined with the significantly larger evoked hemodynamic response observed during anesthesia-related suppressed states, led us to the hypothesis that when tissue is less active, blood vessels are in a more relaxed and compliant state, enabling an increased evoked blood response to stimulation.

Evoked Hemodynamic Responses are Muted after Sleep Deprivation

To further test vascular compliance limits, we measured the evoked hemodynamic response after increasing the amount of sleep deprivation. With increasing deprivation, evoked hemodynamic responses decrease significantly, suggesting that the vessels are stretched to their limit during the deprivation, and that it takes some time to recover (Fig. 5.7). Thus, silent or hyperpolarized periods may be required to restore vessel compliance. However, to understand the mechanisms involved in this response, many more experiments are required to image the dynamics of vascular expansion.

Cytokine and ATP Involvement in Vascular Control

Cytokine molecules such as adenosine, NO, TNF, and IL1 are responsible for changes in blood flow and are also involved in cortical-column state changes, thus linking metabolism, blood flow, and state (Krueger et al., 2008). Cytokines are produced during normal activity as well as during

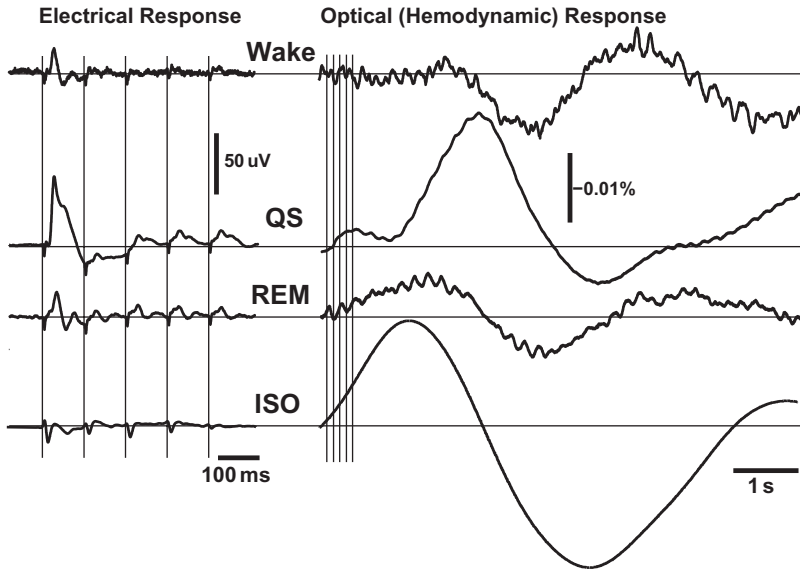

Figure 5.6 The traces in the left panel illustrate typical electrical evoked responses during auditory stimulation during Wake, quiet sleep (QS), rapid eye movement sleep (REM), and during isoflurane anesthesia. Five consecutive stimuli are presented with 100 ms interstimulus interval (ISI), represented by the vertical lines. Traces in the right panel show the corresponding evoked hemodynamic response as recorded by changes in 660 nm reflect light. The size of both the electrical and optical responses increases during sleep and then decreases back to waking levels during REM sleep. We initially thought that the increased hemodynamic response during sleep was caused by the increased evoked electrical response, however, under isoflurane anesthesia, the electrical response is smaller than during quiet sleep, yet the optical response is much larger than sleep. These results suggest that when baseline neural activity high (wake and REM sleep), the concurrent hemodynamic response is muted due to vascular stretching. We hypothesize that this muted hemodynamic response is due to the possibility that blood vessels are less compliant.

cellular stress, including metabolic deficits. Thus sleep promoting cytokines may be responsible for modulating blood supply to the tissue based on demand by expanding vessels and increasing flow. As the currency for cellular energy, ATP represents the ultimate measure of energy expenditure. When tissue expends energy during the depolarized state, cytokines initiate increased blood volume through vessel expansion until the vessels can no longer supply sufficient metabolites. Increased cytokine production could then trigger cells within the cortical column to enter the hyperpolarized state, both as a neuroprotective mechanism, and to give the cells a chance to restore their energy stores and allow time for vessels to relax.

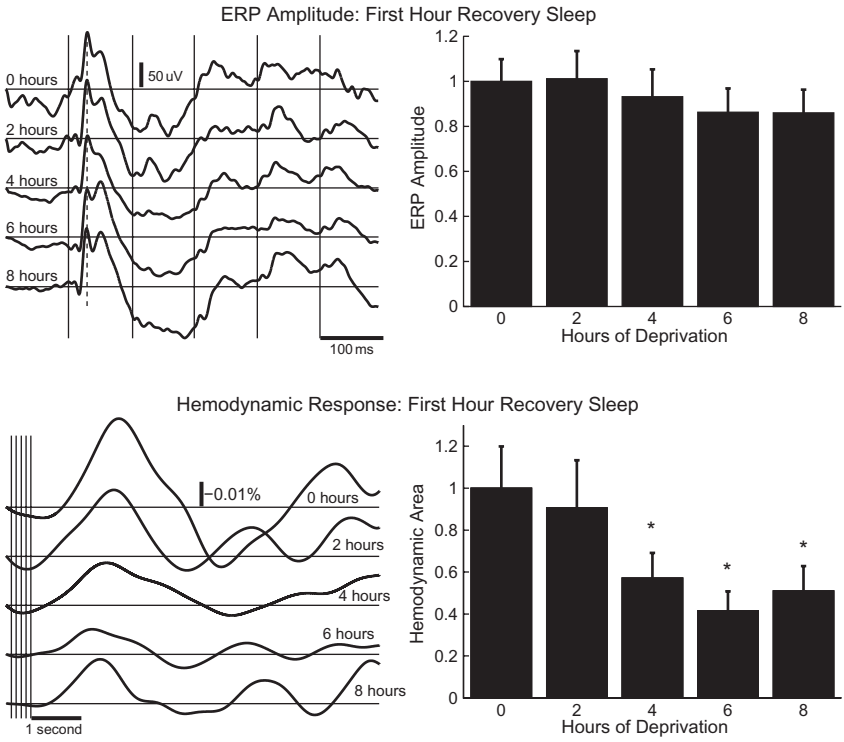

Figure 5.7 To further test possible saturation of the evoked vascular response due to reduced compliance, we subjected animals to sleep deprivation and recorded the evoked electrical and optical responses during subsequent recovery sleep. During the first hour of recovery sleep after sleep deprivation, the electrical evoked response is characteristically large, and does not depend significantly on the amount of prior sleep deprivation. The traces in the upper left panel plot the average electrical evoked response during the first hour of recovery sleep after increasing periods of sleep deprivation from a typical recording. The upper right bar graph depicts the average electrical response following different amounts of sleep deprivation from 12 animals. However, the evoked optical/hemodynamic response is muted with increasing amounts of sleep deprivation (lower panels). These data fit our hypothesis since blood vessels should be more dilated with increasing time awake, and thus the evoked hemodynamic response should be smaller as blood vessels dilate to their maximum volume, resulting in a decreased ability to deliver blood to activated tissue.

CONCLUSIONS

Increasing evidence points to limits in energy stores that relate to sleep need and restoration of these stores during sleep. It is possible that the hyperpolarized/down state is required as a neuroprotective mechanism to prevent metabolite deficit and enable heat removal. Development of

agents to temporarily maintain attention, cellular activity states, and performance may help to keep people awake longer, but the long-term consequences of maintaining alert states may have adverse affects that go far beyond currently studied processes. In particular, if the limits of vascular compliance are constantly reached, metabolic deficit may limit the ability of the tissue to maintain activity levels and process incoming information. More dramatically, chronically reaching these limits over the long term may result in cellular trauma, oxidative stress, and cell death. If maintained over many years, such trauma could lead to decreased brain mass in critical areas that were overused by the person, and subsequent degradation of capacity (Macey et al., 2008).

Arguably, many more experiments are required to test these ideas; however, much evidence has already accumulated in support of the mechanisms proposed here. A focused effort to study vascular compliance across normal and sleep deprived conditions will reveal some important results. The experiments conducted to date recorded blood volume and component changes in response to stimulus evoked changes. However, these are indirect measures of blood vessel compliance. By imaging microvessels directly with implantable microscopy technology (Rector & Harper, 1991), future studies should be able to assess the contributions of blood vessel stretching more directly.

ACKNOWLEDGMENTS

This research was supported by the W.M. Keck Foundation, NIH MH60263, and NIH MH71830.

REFERENCES

Balkin, T. J., Bliese, P. D., Belenky, G., Sing, H., Thorne, D. R., Thomas, M., et al. (2004). Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *Journal of Sleep Research*, *13*(3), 219–227.

Behzadi, Y., & Liu, T. T. (2005). An arteriolar compliance model of the cerebral blood flow response to neural stimulus. *Neuroimage*, *25*(4), 1100–1111.

Benington, J. H., & Heller, H. C. (1995). Restoration of brain energy metabolism as the function of sleep. *Progress in Neurobiology*, *45*(4), 347–360.

Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An $H_2(15)O$ pet study. *Brain*, *120*(Pt 7), 1173–1197.

Buxton, R. B., Uludağ, K., Dubowitz, D. J., & Liu, T. T. (2004). Modeling the hemodynamic response to brain activation. *Neuroimage*, *23*(Suppl. 1), S220–233.

Colrain, I. M., & Campbell, K. B. (2007). The use of evoked potentials in sleep research. *Sleep Medicine Reviews*, *11*(4), 277–293.

Devor, A., Dunn, A. K., Andermann, M. L., Ulbert, I., Boas, D. A., & Dale, A. M. (2003). Coupling of total hemoglobin concentration, oxygenation, and neural activity in rat somatosensory cortex. *Neuron*, *39*(2), 353–359.

Fehm, H. L., Kern, W., & Peters, A. (2006). The selfish brain: Competition for energy resources. *Progress in Brain Research*, *153*, 129–140.

Filosa, J. A., & Blanco, V. M. (2007). Neurovascular coupling in the mammalian brain. *Experimental Physiology*, *92*(4), 641–646.

Grandner, M. A., Patel, N. P., Gehrman, P. R., Perlis, M. L., & Pack, A. I. (2010). Problems associated with short sleep: Bridging the gap between laboratory and epidemiological studies. *Sleep Medicine Reviews*, *14*(4), 239–247.

Grenèche, J., Krieger, J., Erhardt, C., Bonnefond, A., Eschenlauer, A., Muzet, A., et al. (2008). EEG spectral power and sleepiness during 24 h of sustained wakefulness in patients with obstructive sleep apnea syndrome. *Clinical Neurophysiology*, *119*(2), 418–428.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., Peterson, M. J., et al. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nature Neuroscience*, *9*, 1169–1176.

Huppert, T. J., Allen, M. S., Benav, H., Jones, P. B., & Boas, D. A. (2007). A multicompartment vascular model for inferring baseline and functional changes in cerebral oxygen metabolism and arterial dilation. *Journal of Cerebral Blood Flow and Metabolism*, *27*(6), 1262–1279.

Kattler, H., Dijk, D. J., & Borbely, A. A. (1994). Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *Journal of Sleep Research*, *3*, 1599–1604.

Kavanau, J. L. (1996). Memory sleep and dynamic stabilization of neural circuitry: Evolutionary perspectives. *Neuroscience and Biobehavioral Reviews*, *20*, 289–311.

Koch, C. (2004). *The Quest for Consciousness*. Englewood, Colorado: Roberts and Company.

Krueger, J. M., & Obal, F., Jr. (1993). A neuronal group theory of sleep function. *Journal of Sleep Research*, *2*, 63–69.

Krueger, J. M., Rector, D. M., Roy, S., Van Dongen, H. P., Belenky, G., & Panksepp, J. (2008). Sleep as a fundamental property of neuronal assemblies. *Nature Reviews Neuroscience*, *9*(12), 910–919.

Lydic, R. (1987). State-dependent aspects of regulatory physiology. *The FASEB Journal*, *1*(1), 6–15.

Macey, P. M., Kumar, R., Woo, M. A., Valladares, E. M., Yan-Go, F. L., & Harper, R. M. (2008). Brain structural changes in obstructive sleep apnea. *Sleep*, *31*(7), 967–977.

Mahowald, M. W., & Schenck, C. H. (2005). Insights from studying human sleep disorders. *Nature*, *437*, 1279–1285.

Massimini, M., Rosanova, M., & Mariotti, M. (2003). EEG Slow (~1 Hz) waves are associated with nonstationarity of Thalamo-Cortical sensory processing in the sleeping human. *Journal of Neurophysiology*, *89*, 1205–1213.

Massimini, M., Tononi, G., & Huber, R. (2009). Slow waves, synaptic plasticity and information processing: Insights from transcranial magnetic stimulation and high-density EEG experiments. *The European Journal of Neuroscience*, *29*(9), 1761–1770.

McGinty, D., & Szymusiak, R. (1990). Keeping cool: A hypothesis about the mechanisms and functions of slow-wave sleep. *Trends in Neurosciences*, *13*(12), 480–487.

Penfield, W. (1958). Functional localization in temporal and deep sylvian areas. *Research Publications – Association for Research in Nervous and Mental Disease*, *36*, 210–226.

Phillips, D. J., Schei, J. L., Meighan, P. C., & Rector, D. M. (2011). Cortical evoked responses associated with arousal from sleep. *Sleep*, *34*(1), 65–72.

Phillips, D. J., Schei, J. L., Meighan, P. C., & Rector, D. M. (2011). State-dependent changes in cortical gain control as measured by auditory evoked responses to varying intensity stimuli. *Sleep*, *34*(11), 1527–1537.

Pigarev, I. N., Nothdurf, H. C., & Kastner, S. (1997). Evidence for asynchronous development of sleep in cortical areas. *Neuroreport*, *8*, 2557–2560.

Rector, D., & Harper, R (1991). Imaging of hippocampal neural activity in freely behaving animals. *Behavioural Brain Research*, *42*(2), 143–149.

Rector, D. M., Topchiy, I. A., Carter, K. M., & Rojas, M. J. (2005). Local functional state differences between rat cortical columns. *Brain Research*, *1047*, 45–55.

Rector, D. M., Schei, J. L., & Rojas, M. J. (2009a). Mechanisms underlying state dependent surface-evoked response patterns. *Neuroscience*, *159*, 115–126.

Rector, D. M., Schei, J. L., Van Dongen, H. P., Belenky, G., & Krueger, J. M. (2009b). Physiological markers of local sleep. *The European Journal of Neuroscience*, *29*(9), 1771–1778.

Roy, S., Krueger, J. M., Rector, D. M., & Wan, Y. (2008). Network models for activity-dependent sleep regulation. *Journal of Theoretical Biology*, *253*, 462–468.

Roy, C. S., & Sherrington, C. (1890). On the regulation of the blood supply of the brain. *The Journal of Physiology*, *11*, 85–108.

Saper, C. B., Chou, T. C., & Scammel, T. E. (2001). The sleep switch: Hypothalamic control of sleep and wakefulness. *TINS*, *24*(12), 726–731.

Szymusiak, R., & McGinty, D. (2008). Hypothalamic regulation of sleep and arousal. *Annals of the New York Academy of Sciences*, *1129*, 275–286.

Shaw, G. L., Harth, E., & Scheibel, A. B. (1982). Cooperativity in brain function: Assemblies of approximately 30 neurons. *Experimental Neurology*, *77*(2), 324–358.

Schei, J. L., Foust, A. J., Rojas, M. J., Navas, J. A., & Rector, D. M. (2009). State-dependent auditory evoked hemodynamic responses recorded optically with indwelling photodiodes. *Applied Optics*, *48*(10), D121–D129.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, *262*, 679–685.

Steriade, M., Timofeev, I., & Grenier, F. (2001). Natural waking and sleep states: A view from inside neocortical neurons. *Journal of Neurophysiology*, *85*, 1969–1985.

Sherrington, C. S. (1951). *Man on his nature* (2nd ed.). Cambridge, MA: Cambridge University Press.

Timofeev, I., Contreras, D., & Steriade, M. (1996). Synaptic responsiveness of cortical and thalamic neurones during various phases of slow sleep oscillation in cat. *The Journal of Physiology*, *494*(1), 265–278.

Van Dongen, H. P., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, *26*(2), 117–126.

Vyazovskiy, V. V., Olcese, U., Lazimy, Y. M., Faraguna, U., Esser, S. K., Williams, J. C., et al. (2009). Cortical firing and sleep homeostasis. *Neuron*, *63*, 865–878.

Weitzman, E. D., & Kremen, H. (1965). Auditory evoked responses during different stages of sleep in man. *Electroencephalography and Clinical Neurophysiology*, *18*, 65–70.

Wesensten, N. J., Belenky, G., Thorne, D. R., Kautz, M. A., & Balkin, T. J. (2004). Modafinil vs. caffeine: Effects on fatigue during sleep deprivation. *Aviation, Space, and Environmental Medicine*, *75*(6), 520–525.

Yasuda, T., Yasuda, K., Brown, R. A., & Krueger, J. M. (2005). State-dependent effects of light-dark cycle on somatosensory and visual cortex EEG in rats. *The American Journal of Physiology*, *289*, R1083–R1089.