Sleep Medicine 15 (2014) 279–288

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Role of cardiorespiratory synchronization and sleep physiology: effects on membrane potential in the restorative functions of sleep

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 18 October 2013
Accepted 19 October 2013
Available online 30 January 2014

Keywords:
Cardiorespiratory synchronization
Autonomic nervous system
Membrane potential
Restoration
Sleep neuroanatomy
Sleep physiology

ABSTRACT

Although sleep physiology has been extensively studied, many of the cellular processes that occur during sleep and the functional significance of sleep remain unclear. The degree of cardiorespiratory synchronization during sleep increases during the progression of slow-wave sleep (SWS). Autonomic nervous system (ANS) activity also assumes a pattern that correlates with the progression of sleep. The ANS is an integral part of physiologic processes that occur during sleep with the respective contribution of parasympathetic and sympathetic activity varying between different sleep stages. In our paper, we attempt to unify the activities of various physiologic systems, namely the cardiac, respiratory, ANS and brain, during sleep into a consolidated picture with particular attention to the membrane potential of neurons. In our unified model, we explore the potential of sleep to promote restorative processes in the brain.

1. Introduction

Although numerous studies have investigated its purpose, a complete picture of the physiologic role of sleep is still unclear. Numerous theories for the primary function of sleep have been proposed, though none have gained sufficient experimental evidence to earn substantial support from the sleep research community [1]. However, many proposed theories restrict the beneficial impact of sleep to specific physiologic processes, which might not allow a complete understanding of the global impact of sleep on the body [2]. It is clear that sleep serves as a restorative function, and the deleterious effects of sleep deprivation are well-documented [3].

Previous studies have established a correlation between neural restoration and sleep regularity. Other forms of restoration in the body also have been observed, but much less evidence supports the notion that sleep provides primarily somatic as opposed to neural restoration [1]. A growing consensus suggests that a major benefit of sleep involves ongoing support for neuronal function in the brain. However, this agreement does not exclude the possibility that other physiologic systems are employed to serve this restorative purpose. For example, cardiorespiratory synchronization that occurs during slow-wave sleep (SWS) in the form of respiratory sinus arrhythmia (RSA) and cardiorespiratory phase synchronization can employ the heart and lungs to assist in the restorative functions of sleep [4]. The degree of synchronization between the heart and lungs may indicate the depth and quality of sleep [5]. This synchronization leads to a shift in the sympathovagal balance during the sleep cycle which can help modulate the membrane potential of neurons, helping to restore optimal function and replenish neurons with crucial supplies for energy [6]. Synchronization also may account for the biologic activity of neurotransmitters and signaling by nuclei of the hypothalamus and brainstem. Future research that focuses on cardiorespiratory synchronization and the modulation of neuronal membrane potential could provide a more accurate model for the function of sleep in both the brain and the body as a whole.

During SWS, membrane potential signaling in the brain is dominated by inhibition, and inhibition has been found to be the biggest contributor to changes in membrane potential. It is likely that inhibition and hyperpolarization processes play an important role during sleep [7]. During SWS, the cortex and subcortical structures like the thalamus, hypothalamus, amygdala, and reticular activating system are globally inhibited and are under strong hyperpolarizing forces [8].

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http://dx.doi.org/10.1016/j.sleep.2013.10.017
1389-9457/

2. Cardiorespiratory synchronization and autonomic nervous system modulation in sleep

The activities of the heart, respiration, and the autonomic nervous system (ANS) vary between sleep stages [9,10]. The changes in the activity and pattern of these systems are consistent as the stages of sleep progress. Respiration becomes deeper and slower during nonrapid eye movement (NREM) sleep, especially SWS sleep, while breathing becomes more shallow and frequent during rapid eye movement (REM) sleep [11]. Heart rate decreases during NREM sleep and increases throughout periods of REM sleep [12,13]. Reductions in slow spontaneous oscillations in hemodynamics usually present in wakefulness and REM sleep due to increased sympathetic tone also occur during SWS sleep in both cerebral and systemic blood flow [14]. The observed reductions in heart rate, respiration, and blood pressure usually are attributed to a reduction in the metabolic demands of the body and brain [12].

The cyclical changes of the ANS during the sleep cycle accurately reflect those of the heart. During NREM sleep, parasympathetic activity dominates vagal outflow to the heart and body, though REM sleep shows a shift to a more predominate sympathetic influence [5,11,15]. ANS activity is commonly measured during sleep using heart rate variability (HRV) as a noninvasive index of parasympathetic or sympathetic output [16]. A high frequency of variability in beat-to-beat intervals (RR intervals) is indicative of parasympathetic influence on the heart, though low variability coincides with sympathetic activation [17,18]. HRV measurements also can provide a measure of cardiorespiratory synchronization [19].

The concomitant decreases in heart and breathing rates mediate synchronization between heart and respiration. A reduced rate in respiration acts to induce a synchronization of the ANS input and heart rate pattern through activation of the parasympathetic branch of vagus nerve afferents [20–23]. The manifestation of such synchronization is RSA, during which the beat-to-beat intervals of heart rate coincide with respiration [24]. RSA has been shown to continue during sleep states [25]. An additional form of cardiorespiratory coupling provides another measure of the extent of synchronization between the heart and breathing patterns. This form of synchronization is termed *cardiorespiratory phase synchronization* and is defined as breathing cycles and heart beats occurring in the same relative phase for prolonged periods [26,27].

The relationship between cardiorespiratory synchronization and ANS activity during sleep has been well-characterized. Cardiorespiratory phase synchronization coincides with a high level of parasympathetic activity and reaches a plateau during NREM sleep [5,26,28]. In contrast, little to no synchronization occurs during REM sleep [26,28]. Research has shown increasing levels of synchronization throughout NREM sleep with 3 to 1, 4 to 1 (most common), 5 to 1, and even 6 to 1 ratios of cardiac rate to breathing rate during the deepest sleep [28,29]. An increase in various markers of HRV and HRV frequency is closely related to sleep stage progression [30]. This intimate interaction between heart activity and respiration has been observed in individuals of all ages [31–35]. Current evidence from studies examining the impact of slow deep breathing on ANS function suggests that a shift in sympathovagal balance during sleep mediates the synchronization between the heart and lungs [36–39].

In addition, several studies have shown a strong interaction between parasympathetic vagal activity of the heart and the delta and slow waves (electroencephalogram [EEG]) occurring during SWS [33,34,40]. This interaction is believed to be a result of the high frequency of variability in RR intervals during NREM sleep, an indicator of cardiorespiratory synchronization, interacting with delta wave oscillations of the brain [12]. Interestingly, vagal effects on heart rate occur before the observed changes in delta activity during EEG recordings [33,34]. Changes in heart rate and autonomic arousal, measured in relation to RR interval and heart activity, are closely related with EEG measurements during sleep and also precede the corresponding EEG changes [41]. A relationship between EEG and heart activity during sleep also has been shown in infants [42,43]. A recent study found that the interactions of delta EEG activity and cardiorespiratory oscillations during anesthesia primarily are mediated by respiration, followed by corresponding cardiac activity [44]. In agreement, additional evidence demonstrates that neuronal delta oscillations in the olfactory bulb couple with respiratory patterns during breathing in mice [45].

The close relationship between the ANS and sleep can be illustrated by the fact that many medical disorders, such as diabetes mellitus, Alzheimer disease, and Parkinson disease (PD), are associated with both autonomic dysfunction and sleep disorders while some primary sleep disorders are associated with ANS problems [46]. Insights into the importance of cardiorespiratory synchronization during sleep can be gained through the study of sleep apnea, a disorder that impairs breathing. Obstructive sleep apnea (OSA) is marked by the occurrence of regular cessations in breathing that last at least 10 s, but normally 30–60 s, due to the collapse of upper airways during sleep [13]. During apnea episodes, a bradycardia rhythm of the heart occurs followed by a tachycardia at the end of apnea. This pattern has been attributed to parasympathetic control of the heart, interrupted by sympathetic arousal at the end of the apnea [47]. This continuous arousal throughout sleep, though not enough to cause waking, impairs cardiorespiratory synchronization [12,29] and leads to daytime sleepiness from sleep fragmentation [13]. A study by Kabir et al. [29] found that participants with OSA had far less cardiorespiratory synchronization during sleep than those without OSA. We propose that these daytime effects are due in part to the lower levels of synchronized cardiac and respiratory signals that occur, leading to less hyperpolarization and inhibition.

More severe effects of apneas also have been discovered. Research shows that apnea or hypopnea patients have increased levels of sympathetic nerve activity [48], as well as increased risk for cardiovascular disease [49–52]. In addition to apnea sleep disorders, patients who report primary insomnia have reduced cardiorespiratory coupling during sleep and poor sleep quality [53]. Atrial fibrillation, though related to cardiac activity rather than respiration, also impairs sleep. Patients with atrial fibrillation, a common disturbance of normal cardiac rhythm, have been shown to exhibit a significantly poorer quality of sleep compared to control participants [54]. Such a disturbance in the normal heart rhythm likely impairs the amount of cardiorespiratory synchronization possible. In the study [54], correcting the atrial fibrillation and restoring sinus arrhythmia led to an improved sleep quality score, likely due in part to the restoration of cardiorespiratory synchronization. Sleep disorders are common among PD patients [55] and individuals with PD also have been found to experience less cardiorespiratory synchronization than healthy patients [56]. Studies on cardiorespiratory synchronization in patients with other autonomic disorders are lacking, but these studies suggest that some of the restorative effects of sleep may be due to cardiorespiratory synchronization.

Although it is understudied and not well understood, a regular nightly occurrence of cardiorespiratory synchronization and the negative effects correlated with decreased synchronization during sleep suggest an important role for cardiorespiratory synchronization in the function of sleep. Although it may not be the primary function, the observed synchronization between the heart and lungs may provide a means to serve other functions associated with sleep. We suggest that cardiorespiratory synchronization allows the neuronal membrane potential to be regenerated through an autonomic shift towards the parasympathetic state.