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Sleep Medicine 6 Suppl 1 (2005) S8–S12

SLEEP MEDICINE

www.elsevier.com/locate/sleep

The neuro-biomolecular basis of alertness in sleep disorders

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Abstract

Sleep is present in all species in which it has been studied, but its functions remain unknown. Identification of the molecular correlates of sleep and wakefulness is essential if we are to understand the restorative processes that occur during sleep, the cellular mechanisms that underlie sleep regulation, and the functional consequences of sleep loss and poor quality sleep. To address the questions of how we know whether sleep has performed its functions and whether treatment has improved sleep quality, we have proposed a synaptic homeostasis hypothesis about the significance of slow wave activity (SWA) during sleep and its homeostatic regulation. Briefly, the hypothesis states that (1) wakefulness is associated with potentiation in several cortical circuits; (2) synaptic potentiation is then tied to the homeostatic regulation of SWA; (3) SWA is associated with synaptic downscaling; and (4) synaptic downscaling is tied to the beneficial effects of sleep on performance. According to this hypothesis, the potentiation of neural circuits that results from synaptic plasticity during alert wakefulness is responsible for SWA homeostasis. Increasing noradrenergic activity increases the expression of long-term potentiation (LTP)-related genes, and interference with these changes block the induction of markers of synaptic potentiation during alert wakefulness. Inducing local LTP-like changes during alert wakefulness also results in increased local slow wave homeostasis. Thus, as SWA homeostasis can be induced on a local level or can be triggered by a learning task, and is strongly correlated with postsleep performance enhancement, plasticity during alert wakefulness depends on good sleep, which, in turn, depends on efficient synaptic downscaling.

Keywords: Synaptic homeostasis; Neural circuits; Sleep function; Long-term potentiation; Slow-wave activity; Plasticity; Noradrenergic system

1. Introduction

Sleep is present in all species in which it has been studied, but its functions remain unknown. Evidence that sleep clearly serves fundamental functions comes from studies that show that sleep deprivation in humans leads to overwhelming sleep pressure, impaired alertness and performance, and physiological deficits [1–3]. It has also been shown that prolonged sleep deprivation in rats [4] and flies [5] is fatal. However, to determine whether sleep has performed its function and whether treatment has improved it, the functions of sleep need to be elucidated. Identification of the molecular correlates of sleep and wakefulness is essential if we are to understand the restorative processes that occur during sleep, the cellular mechanisms that underlie sleep regulation, and the functional consequences of sleep loss and poor quality sleep. Furthermore, the development of pharmacological solutions to reduce the need for sleep or improve sleep quality requires knowledge of the basic mechanisms and functions of sleep. Specifically, the identification of new targets for drug development requires a mechanistic understanding of how sleep is regulated at the cellular and molecular levels.

Currently, two approaches are used to gain insight into the function of sleep; one is to examine performance and health benefits of different sleep and treatment regimens, and the other is to formulate hypotheses about sleep function in order to gain scientific understanding of what sleep should be doing and whether it has been effective, especially in promoting alertness during waking hours. In humans and other mammals, the increased need to sleep after extended periods of wakefulness is reflected in an increase in slow wave activity (SWA) in the electroencephalogram (EEG) [6]. This is the well known process S, which is the relationship between the duration of wakefulness and increase in slow wave amplitude in the first stage of sleep [7]. However, the aspect of wakefulness responsible for the increased need for sleep remains unknown, and the causes of the increase in SWA and its

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1389-9457/$ - see front matter

function also remain unclear. We recently proposed a synaptic homeostasis hypothesis based on the significance of SWA during sleep and its homeostatic regulation [8]. Briefly, the hypothesis states that (1) wakefulness is associated with potentiation in several cortical circuits; (2) synaptic potentiation is then tied to the homeostatic regulation of SWA; (3) SWA is associated with synaptic downscaling; and (4) synaptic downscaling is tied to the beneficial effects of sleep on performance. According to this hypothesis, the potentiation of neural circuits that results from synaptic plasticity during alert wakefulness is responsible for SWA homeostasis.

Recently, numerous experimental studies have shed light on this complex process by showing that specific transcripts, especially immediate early genes, are rapidly induced in brain neurons in response to synaptic activity during wakefulness, irrespective of circadian timing [9–11]. This report examines several lines of evidence that support a link between sleep and synaptic homeostasis and proposes some testable predictions to determine whether the functions of sleep may relate to cellular and molecular aspects of neuronal function.

2. Sleep and synaptic homeostasis hypothesis

In the cerebral cortex there are approximately 30 billion neurons with about 10,000 synapses impinging on each neuron. During the day, learning and adaptation to the environment produces synaptic strengthening in all circuits of the cerebral cortex and other parts of the brain. By the end of the day, a very large amount of synaptic potentiation has occurred in all brain circuits. This is associated with very high energy costs, because almost 80% of the energy needs of the brain are to support synaptic activity; space costs, because there is no room to add more synapses; and risk for neuron saturation due to the increase in the number of synapses. If the synapses are 30% stronger on average all over the brain, it is very difficult metabolically to stay awake, alert and learn (Fig. 1). A mechanism is needed to avoid progressive saturation of the synapses.

The size of slow waves that occur just after sleep onset depend on synaptic strength at the end of the day, which in turn depends on the amount of time spent awake, learning and modifying the circuits. As slow waves are regulated as a function of previous wakefulness, we postulate that the role of slow waves is synaptic downscaling or a decrease in the strength of synapses (Fig. 1). Consequently, by the morning after a night of sleep, the slow waves have decreased in amplitude because the synapses have become weaker and returned to their normal baseline level. The next day after a night of sleep, it is possible to start learning again due to the energy and space savings and increases in signal to noise ratio. This explains the increase of SWA after synapatic potentiation and suggests that the function of sleep is to get all the synapses leaner and efficient after a day of wakefulness.

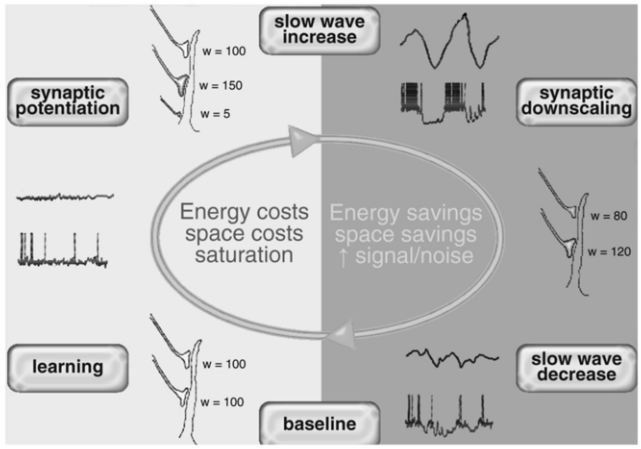

Fig. 1. From Tononi G, Cirelli C. Brain Res Bull 2003.

3. Gene expression during wakefulness and sleep

Genes involved in synaptic potentiation are induced in the cerebral cortex and hippocampus during alert wakefulness but not during sleep, and are thus molecular markers of these behavioural states. A study has shown that NGFI-A, an immediate early gene often associated with synaptic or long-term potentiation (LTP), is highly expressed all over the brain during waking but is reduced to very low, almost minimal levels during sleep [12]. Phosphorylated CRE-binding protein (P-CREB) has also been shown to play a necessary role in LTP in various models. In sleep-deprived animals, CREB activates the transcription of CRE-driven genes and leads to a cell-wide distribution of proteins that prime the synapses for subsequent synapse-specific capture of late-phase LTP, which may be sufficient for consolidation of LTP [13]. Another study has shown that as inhibition of Arc expression impairs the maintenance phase of LTP without affecting its induction, Arc appears to play a fundamental role in the stabilization of activity-dependent hippocampal plasticity [14].

Brain-derived neurotrophic factor (BDNF) is also expressed at high levels during waking and low levels in sleep, and is another candidate for LTP and synaptic plasticity thought to have a functional role in the expression of LTP in the hippocampus [15,16]. Homer proteins and Narp (neuronal activity-regulated pentraxin), both of which are also high in sleep deprivation and spontaneous awakening and very low during sleep, are newly studied molecules that appear to have a crucial role in the clustering of receptors where synaptic strengthening occurs. A study of Homer proteins [17] has shown that the number of neurotransmitter receptors in the postsynaptic membrane and their functional coupling to intracellular signalling cascades are important determinants of synaptic strength, and hence are potential targets for plasticity-related modulation. Also, as Narp transgenic expression increases