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Review Article

Two features of sleep slow waves: homeostatic and reactive aspects – from long term to instant sleep homeostasis

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ABSTRACT

In this paper we reviewed results of sleep research that have changed the views about sleep slow wave homeostasis, which involve use-dependent and experience-dependent local aspects to understand more of the physiology of plastic changes during sleep. Apart from the traditional homeostatic slow-wave economy, we also overviewed research on the existence and role of reactive aspects of sleep slow waves. Based on the results from spontaneous and artificially evoked slow waves, we offer a new hypothesis on instant slow wave homeostatic regulation. This regulation compensates for any potentially sleep-disturbing events by providing instant "delta injections" to maintain the nightly delta level, thus protecting cognitive functions located in the frontal lobe. We suggest that this double (long-term /instant) homeostasis provides double security for the frontal lobes in order to protect cognitive functions. The incorporation of reactive slow wave activity (SWA) makes sleep regulation more dynamic and provides more room for the internalization of external influences during sleep.

1. Introduction

1.1. Slow waves and sleep homeostasis

1.1.1. Wake/sleep dependent slow waves and sleep homeostasis

The recognition of slow waves known as delta (D) waves (standing for disease, degeneration, and death according to the classical electroencephalography or EEG terminology) is attributed to the work of William Gray Walter, one of the pioneers of brain research, in the 1930s [1]. The strong link between slow waves and sleep was first reported by Alfred Lee Loomis in the 1930s [2]. He also described the increase in the amplitude of delta waves over the course of wake–sleep transition until reaching deep sleep. Most important he also recognized the reactive nature of slow waves and accurately described the K-complexes evoked by knocking on the sleepers' door (K standing for 'knock'). Pappenheimer et al. [3], while searching for a physiological measure for sleep deprivation-induced sleep rebound, recognized that the best measure is sleep EEG slow wave activity.

The classical frequency range for delta waves was considered to be 1–4 Hz. The two-process sleep model of Borbély was based on power spectrum calculations estimating slow waves in the range of 0.75–4.5 Hz [4]. Steriade and co-workers later published a series of papers [5–7], reporting that the cellular processes contributing to delta waves (<4 Hz) are not homogeneous, and the 0.1–1 Hz component of the delta (<4 Hz) activity has distinct cellular substrates which are of utmost importance in sleep rhythm generation. They also reported that the 0.1–1 Hz waves reflect large-scale, rhythmic hyperpolarizations followed by widespread depolarization. They showed that the hyperpolarization–depolarization sequences originate from cortical neurons and are synchronized by cortico-cortical connections. According to this framework, the 1–4 Hz waves reflect thalamic clock-like delta activity and cortical delta activity, while the <1 Hz component is solely of cortical origin and reflects different physiological processes [8]. A detailed description of sleep rhythm generation in the thalamocortical system was also given. This suggested model was based on the hypothesis that the hyperpolarization-rebound sequences of thalamocortical feedback loops generating spindle and delta waves are triggered and grouped by the depolarization phases (up states) of slow oscillation [7].

The distinction between slow oscillation and delta waves was confirmed by the sleep recordings performed in animal models lacking T-type Ca^{2+} channels. The lack of this channel resulted in a significant decrease of delta and spindle oscillations, but not of slow (<1 Hz) oscillation, which remained unaffected [8].

Other molecular evidence for the differentiation between slow oscillation and delta waves has come from pharmaco-EEG studies of sleep. Benzodiazepine hypnotics decrease non-rapid eye

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movement (NREM) sleep EEG power in the delta range (>1 Hz), but may significantly increase the slower (<1 Hz) frequency components [9]. Moreover, only low EEG frequencies (<1.5 Hz), but not higher frequency delta activity, are affected by noradrenaline depletion in sleep-deprived rats: neurotoxic lesions with DSP-4 reduce 0.5–1.5-Hz activity in recovery sleep, while >1.5-Hz activity remains unchanged [10].

At this point we should mention that animal models have limited validity in this review since frontal lobes, which play a crucial role in slow wave oscillations during sleep, are underdeveloped in animals. Also, the significance of the different EEG frequency bands can be profoundly different in humans and other mammals.

Slow waves have gained importance particularly since the recognition of homeostatic regulation of sleep by Wilse Webb [11] and Feinberg et al. [12], and the integration of the theory into a mathematical model by Borbély and co-workers in the 1980s [4,13]. They have shown that the depth of sleep measured by power of 0.75–4.5 Hz slow wave activity is related to the duration of preceding wakefulness. Dijk et al. [14] have shown that an exponential increase of delta power is apparent during daytime naps, while nocturnal sleep is characterized by an exponential decrease of delta power throughout the night. The presence of a slow wave rebound after sleep deprivation [3,4] strongly indicates that there is a biological need for slow waves, and that the homeostatic regulating mechanism of slow waves serves this need.

Thanks to the above mentioned pioneers who revealed the nature of sleep homeostasis 30 years ago, we learned that slow waves are precisely regulated in sleep/wakefulness, and this 'slow-wave economy' certainly has an important role. However, until recently it was not clear which factors exponentially increase the amount of slow waves during the day and what kind of physiological processes take place when the increased slow waves exponentially decay during sleep.

1.1.2. A precise slow wave economy and sleep homeostasis

Although the time course of delta activity is characterized by a steeper decline over the sleep cycles (NREM periods) than the time course of the slow oscillations, in physiological conditions both seem to be under precise homeostatic regulation [15]. Slow wave oscillations (<1 Hz) have two phases: hyperpolarization (negative values measured by surface EEG), during which cortical neurons are mostly silent, and depolarization (positive values measured by surface EEG), during which most cortical neurons fire intensively [16,17]. There is evidence for the importance of the relationship between the length of these hyper- and de-polarized phases and homeostatic regulation. Under high homeostatic pressure, short periods of depolarized phases alternate with long periods of hyperporalized phases. Conversely, under low homeostatic pressure, long depolarized phases are interrupted by short hyperpolarized phases [18]. Thus, high homeostatic pressure promotes longer hyperpolarization periods. Additionally, it has been shown that higher homeostatic pressure is associated with higher slow wave density, higher amplitudes, and steeper slopes of the down-states of slow oscillations (<1 Hz) [19–22].

1.1.3. Changing concepts of sleep homeostasis – I: from global to local sleep

Over the last 15–20 years, local aspects of homeostatic sleep regulation have received more and more attention. The first explicit statements about the nature of local sleep were delivered by Krueger and Obál [23]. In their work they provided indirect and direct evidence indicating that cortical columns oscillate between functional states defined by changing input–output relationship, as shown by the changing amplitudes of evoked responses. Mosaics of sleeping columns can be found while other columns are awake. The longer a column is in awake-like state, the higher the probability that it will switch to its sleeping mode. The probability of finding sleeping columns also depends on the amount of afferent activity or on neuronal signals as a result of learning. Krueger et al. [24] later emphasized that sleep is a statistical phenomenon, e.g., a sum of the local sleep processes leading to global/behavioral sleep if there is a sufficiently high number of neural networks involved. In this view, local sleep differentiates the state of the different cortical columns. They suggest that the global coordination of NREM is not due to a single sleep generator, but may reflect an emergent property of loosely coupled local processes.

Recent data on the functional organization of brain connectivity during sleep, as evaluated by the use of graph theory tools, have shown significant small-world network features [25,26]. Several studies have demonstrated that the recovery increase of slow-wave activity originates from frontal areas, where it is also the most prevalent [27–30].

There has been an early evidence for the role of slow-wave sleep in human frontal cognitive functions [31]. Achermann et al. [32] called attention to another site-specific feature: the dominant hemispheric prevalence in the slow wave activity (SWA) rebound following, possibly reflecting a feature of speech functions.

Local sleep regulation is a crucial point in understanding the nature of sleep homeostasis. The original two-process model and its later corrections [4,33] focused only on global aspects of the process. However, it is evident from the above-cited studies that local differences are significant and robust enough for considering their involvement in the global aspect of sleep regulation or sleep need. According to this view, sleep regulation centers are "just" coordinators, providing a more or less synchronized entry of many different networks into the sleep state. Sleep-inducing centers, like the ventrolateral preoptic region, are not sleep inducers per se, but synchronizers of many local sleep needs.

1.1.4. Changing concepts of sleep homeostasis – II: from wake-dependent, through use-dependent, to experience-dependent sleep

Later, when local aspects of sleep regulation were increasingly evident, the concept of wake-dependency was slowly completed with the notion of use-dependency, which is in fact based on the amount of afferent inputs to a certain neural network. Beside the frontal lobes involved in the homeostatic regulation related to certain cognitive functions and the dominant hemisphere of speech areas, a use-dependent increase of SWA has been observed in other brain regions after their targeted use. One of the most convincing ones is when extensive sensory stimulation of one hand before sleep led to an increase in sleep delta power in the opposite hemisphere over the somatosensory arm area [34]. An opposite intervention, immobilization of the arm, caused a local reduction of delta power in the same area [35]. Similar results were found in rats after cutting their whiskers on one side and analyzing the changes in hemispheric asymmetry in their sleep SWA [35].

These studies clearly showed that it is a set of specific physiological correlates of sensory stimulation which require some kind of recuperation, not simply the amount of wakefulness. Furthermore, this demand is reflected by the increase in slow wave power during daytime naps/nighttime sleep, and the assumed recuperation is possibly connected with the overnight decay of slow wave activity in sleep.

The importance of the quality of wakefulness – the amount of new experiences that subjects faced during wakefulness – was also shown to alter subsequent slow-wave sleep in a field study of Horne and Minard [36]. Subjects of the experiments of this study were unexpectedly involved in different playful activities: they had a car journey to another city, they visited a large exhibition center and a museum, and they were invited to a whole-day program in an amusement park and a zoo, instead of boring paper-and-pencil tests. Although physical activity was not enhanced during these programs, its effect on the subsequent slow-wave sleep was evident during the sleep laboratory examination [36].

The above study was in fact a forerunner of experiments which demonstrated that it is learning and synaptic plasticity – or