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Sleep and synaptic changes

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Several recent studies, using molecular, electrophysiological, or structural approaches, have investigated how synapses are affected by sleep, spontaneous wake, chronic sleep restriction, and acute sleep deprivation. Overall, the results have found that even a few hours of sleep or wake can modify the molecular composition of excitatory synapses, change their efficacy, and make synapses grow or shrink. Moreover, partial and total loss of sleep affect the ability of synapses to undergo long-term potentiation, an effect that may underlie some of the negative consequences of sleep deprivation on memory and other cognitive functions.

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Introduction

Acute total sleep deprivation and chronic sleep restriction consistently lead to impairment of many cognitive functions, from attention and working memory to verbal fluency, innovative thinking, and even humor appreciation [1,2]. The human brain uses up to 25% of the whole body glucose consumption, despite accounting for only 2% of body mass [3]. Most of this energy is used to sustain the various components of synaptic activity, from the release of neurotransmitter vesicles and their recycling to the restoration of Na^+ and K^+ gradients following postsynaptic potentials [4,5]. It is not surprising, therefore, that many hypotheses about the functions of sleep have focused on its effects on synapses, suggesting that sleep may allow the recovery of the synapses that underwent plastic changes during wake [6], the further strengthening of the synapses activated by learning during wake [7], the stimulation of the synapses that were not sufficiently activated during wake [8–10], or the generalized downregulation of synaptic strength after wake-induced synaptic potentiation [11]. Irrespective of the specific hypothesis, the underlying assumption is that sleep, or lack of it, will affect how synapses work, with significant consequences for brain functions. A brief summary of some of the recent studies that assessed the effects of sleep, wake, and sleep deprivation on synaptic activity is given below.

Molecular changes at the synapse during sleep and wake

Over the last decade, microarray studies have shown that there are hundreds of genes whose brain expression is affected by sleep and wake, and several of them are involved in synaptic plasticity. In general, putative markers of synaptic potentiation, including several immediate early genes and brain derived neurotrophic factor (BDNF), are expressed at higher levels during spontaneous wake and short sleep deprivation than during sleep [12–15,16••]. Most of these studies pooled transcripts from large brain regions, for example the entire cerebral cortex or the whole forebrain, and thus the results suggest that sleep/wake effects on the expression of genes involved in synaptic plasticity are widespread. Other studies [17–19] used rats previously subjected to lesions of the locus coeruleus, to deplete the cerebral cortex of noradrenergic fibers. In general, loss of sleep is followed by a sleep rebound, that is, sleep is longer and deeper, an homeostatic response that strongly suggests that sleep has important functions. The rats with noradrenergic lesions showed a blunted homeostatic response after sleep deprivation. In these animals most cortical transcripts upregulated by wake and short sleep deprivation were unaffected by the noradrenergic depletion, with the exception of plasticity-related genes, whose upregulation during wake was reduced or completely eliminated. These findings suggested that the diffuse upregulation of plasticity-related genes during wake is not just an epiphenomenon of wake-related learning, but may be causally involved in determining sleep need. This conclusion has been strengthened by the results of a recent study [15••] whose results are complementary to those reported in rats with noradrenergic lesions. The authors assessed sleep homeostatic mechanisms and sleep/wake-dependent brain gene expression in normal mice and in mice subjected to adrenalectomy, which abolishes the increase in corticosterone levels often seen during acute sleep deprivation. They found that most of the brain transcripts upregulated after a few hours of sleep deprivation in controls were no longer upregulated in adrenalectomized, sleep deprived mice. Crucially, however, genes involved in synaptic plasticity were among the few still upregulated after adrenalectomy [15••]. Moreover, adrenalectomy did not blunt the sleep homeostatic response; in other words, adrenalectomized mice still

slept deeper and longer after acute sleep deprivation, and did so in a manner indistinguishable from that of controls. Together, the recent study [15••] and the older experiments suggest that sleep need is more strongly linked to the wake-dependent expression of plasticity-related genes than to the expression of other genes controlled by the classical stress pathway.

Most plasticity-related genes identified by microarray studies are only indirect markers of synaptic function. Recent studies, however, have measured how sleep and wake affect the number and phosphorylation levels of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs [20–22,23••]). The occurrence of synaptic potentiation and depression is believed to depend on the movement of AMPARs in and out of the synaptic membrane, respectively [24,25]. AMPARs containing the subunit GluA1 are permeable to calcium and their expression shows a supralinear relationship with the area of the post-synaptic density [26]. Thus, they may be in a unique position to affect synaptic strength. In an early study [20] CA1 neurons in the intact brain were infected with a GluA1-green fluorescent protein (GFP) virus, and hippocampal slices were prepared ~10 hours later, after the rats had spent most of the time either asleep or awake. Only after wake, but not after sleep, CA1 neurons showed increased rectification compared with nonexpressing neurons, indicating synaptic insertion of GluA1-containing AMPARs. GluA2-containing AMPARs, by contrast, could be inserted in both wake and sleep. A more recent study assessed the expression of GluA1-containing AMPARs in synaptoneurosomes, a preparation that enriches for synaptic proteins, and found a ~40% increase in wake relative to sleep in rat cortex and hippocampus [21]. In the same animals absolute levels of GluA1 phosphorylation at Ser831 and Ser845 were also higher in wake than in sleep. GluA1 phosphorylation at Ser831 enhances single channel conductance and is associated with long-term potentiation, while dephosphorylation of GluA1 at Ser845 leads to a decrease in the channel open probability and to internalization of AMPARs [24,25]. Another recent study performed whole-cell patch-clamp recordings from layer V pyramidal neurons of rat somatosensory cortex, and found that after the dark period, when the animals were mostly awake, calcium-permeable AMPA currents accounted for ~25% of the total size of excitatory postsynaptic potentials, while after the light period, which rats spend mostly asleep, their contribution was much reduced, suggesting that GluA1-containing AMPARs are removed during sleep [22]. Finally, it was recently shown, in synaptoneurosomes obtained from mouse cortex (half cortical hemisphere), that GluA1 phosphorylation at Ser845 increases with time spent awake and decreases during sleep [23••]. Thus, in both mice and rats, sleep and wake lead to widespread changes in the expression of AMPARs in both cortex and hippocampus. These changes are consistent with the occurrence of an overall increase in synaptic strength in large brain regions after wake, and an overall decrease after sleep.

Electrophysiological changes at the synapse during sleep and wake

The effects of sleep and wake on electrophysiological markers of synaptic efficacy have also been measured in recent studies. The slope of the early (monosynaptic) response evoked by electrical stimulation delivered *in vivo* is a classical electrophysiological measure of synaptic strength, with a steeper slope indicating higher synaptic efficiency. Studies in rats found that in both cortex [21] and hippocampus [27], the first negative component of the evoked response increases with time spent awake and decreases with time spent asleep. A recent study found similar results in humans using transcranial magnetic stimulation to evoke a response in frontal cortex: the slope of the early response increased progressively in the course of 18 hours of continuous wake, and returned to baseline levels after one night of recovery sleep [28•]. These electrophysiological changes are consistent with the molecular changes described above, pointing to an overall increase in synaptic efficacy after wake. In contrast to these results, a recent study in cats reported that the amplitude of the cortical response increased, rather than decreased, after sleep [29]. Also in contrast to previous studies, whose effects were observed after several hours of sleep or wake, the effect in cats occurred after as little as 10 min of sleep, and rapidly saturated after two short sleep episodes. Whether the saturated responses eventually recovered was not investigated. While species-specific differences may exist, the EEG and intracellular recordings shown in this paper suggest that cats may have been sleepy while the responses were measured, since the membrane potential in the 'awake' condition immediately post-sleep was actually hyperpolarized. In the previous studies in rats and humans, evoked responses were recorded some time after awakening, to avoid confounding effects due to sleep inertia.

The analysis of the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs) in slices is another classical electrophysiological method to assess synaptic strength. It was found that both frequency and amplitude of mEPSCs increase in layers II–III of frontal cortex after wake and short total sleep deprivation, suggesting an increase in both presynaptic and postsynaptic efficacy [30]. In infragranular layers of medial prefrontal cortex, instead, only limited mEPSCs changes were seen after acute sleep restriction that targeted REM sleep but spared 50% of NREM sleep, with a small decrease in amplitude but no change in frequency [31]. Miniature inhibitory postsynaptic currents (mIPSCs) were not affected [31]. This latter study suggests that stronger synaptic effects are seen only when both NREM sleep and REM sleep are prevented.