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RESEARCH HIGHLIGHT

Homeostasis of Synapses: Expansion During Wakefulness, Contraction During Sleep

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Sleep is a universal biological process occurring in almost every species of animal, and the loss of sleep has detrimental effects, especially impairments in cognition [1, 2]. Yet, the neuronal function of sleep is still one of the greatest mysteries.

One prominent idea, known as the synaptic homeostasis hypothesis, suggests that high-frequency neuronal activity during wakefulness results in a global increase in synaptic strengths. This phenomenon is unsustainable, as higher synaptic weights take up more brain volume and consume more energy. The function of sleep, based on this hypothesis, is to reset synaptic strengths [3–5]. Structural evidence for this hypothesis was initially found in *Drosophila*: synaptic size and number enhance during wakefulness and decrease when flies are asleep [6]. Recently, Vivo *et al.* [7] and Diering *et al.* [8] have reported new findings to further support this theory: they found synaptic shrinkage during sleep in mammals and revealed the associated molecular signaling pathways.

Using block-face scanning electron microscopy, Vivo *et al.* directly obtained high-resolution, three-dimensional, ultrastructural images of 6920 synapses during the wake/sleep cycle in mouse primary motor and primary somatosensory cortices. When compared to spontaneous or enforced awake states, the sizes of axon-spine interfaces, the contact areas between axon terminals and dendritic spines, decrease by ~18% during sleep (Fig. 1). Shrinkage in the axon-spine interfaces does not uniformly occur across all synapses, but rather with selective downscaling in 80% of them. The synapses that are downscaled during sleep are small to medium in size, and their spines contain recycling endosomes for enhanced turnover of molecules. As shrinkage of the axon-spine interface indicates weaker synaptic strength, these data support the concept of homeostatic regulation of synaptic strength by sleep.

In addition to morphological changes, Diering *et al.* have also provided evidence of downscaling at the molecular level and identified the underlying machinery. During sleep, synapses contain significantly fewer GluA1 and GluA2 AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) subunits, and show decreased phosphorylation of GluA1. Long forms of the scaffold protein Homer (Homer1L) link metabotropic (m)GluR1/5, inositol 1, 4, 5-trisphosphate receptors (IP3Rs), and protein kinase C (PKC) to form a signaling complex to maintain or enhance synaptic strength. During sleep, a short variant of Homer, Homer1a, is drastically increased at the synapses. As a dominant-negative truncated form of Homer, Homer1a causes the disassembly of the mGluR1/5—Homer1L—PKC/IP3R complex, consequently leading to the removal of synaptic AMPAR subunits (Fig. 1). In addition, the synaptic targeting of Homer1a is oppositely controlled by the wake- and sleep-promoting neuromodulators, noradrenaline and adenosine, implying that Homer1a serves as a crucial molecular integrator of arousal and sleep to control synaptic strength.

Based on the ultrastructural and molecular evidence from these two studies, it is convincing that sleep mainly functions in synaptic homeostasis. Despite this strong evidence, other findings indicate that the functions of sleep are not limited to this process. Memory traces are

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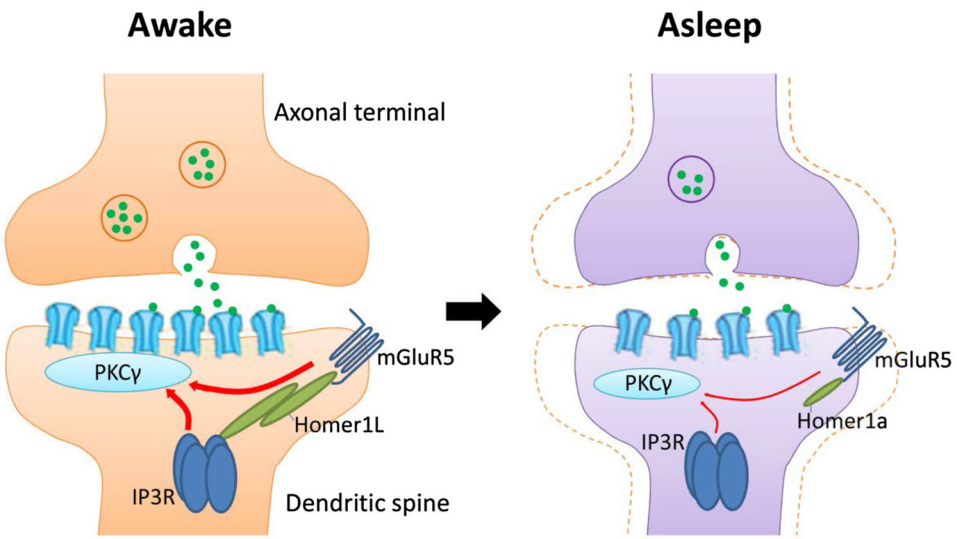

Fig. 1 During sleep, synaptic sizes shrink and glutamate receptor levels decrease. This is driven by the Homer1a-induced remodeling of the mGluR5 signaling complex. *Dashed lines* (right) indicate the profile of the synapse in the awake state.

re-activated during sleep and display specific neuronal oscillation patterns. Offline reactivation enhances learning-related synaptic strength and promotes the formation of new synaptic connections [9]. In addition, rapid eye movement (REM) sleep selectively prunes new synapses after learning, and increases the fraction of learning-induced spines [10]. Even in the studies reported by Vivo *et al.* [7] and Diering *et al.* [8], sleep induces "smart" shrinkage of synapses: not all the synaptic strengths are uniformly reduced, but a small fraction may be upscaled. This complex scenario also implies a memory-consolidation function of sleep.

Overall, in our opinion, there are two main aspects regarding the functions of sleep. One primary function is to restore homeostasis: clearing out metabolic waste products, restoring the sizes of cells and subcellular structures, and healing and repairing damaged cells. These processes occur not only in the brain, but also in peripheral organs, and mainly depend on non-REM sleep. For synapses, sleep-induced renormalization primarily occurs in those that are not involved in memory traces. On the other hand, sleep plays a crucial role in information-processing: memorial information replay, potentiation or deletion of which, to a large extent, may occur during REM sleep. At the synaptic level, information replay might reflect the co-activation of a set of synapses that encode this information during wakefulness. For information potentiation, sleep would effectively increase the sizes and the glutamatergic receptor levels in engram-related synapses, and promote the formation of these synapses. In addition, sleep might also shrink and prune information-related synapses, leading to erasure of the temporal information in buffering areas and facilitate new information-encoding. In any case, definitive investigations of these functions with regard to multiple brain regions and different sleep phases are needed in future studies.

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