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Marcos G. Frank, PhD

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Sleep and plasticity: Waking from a fevered dream

Marcos G. Frank, PhD

Washington State University Spokane
Elson S. Floyd College of Medicine
Department of Biomedical Sciences
Health Sciences Building 280M
412 E. Spokane Falls Blvd.
Spokane WA 99202
PH: 509 368 6747
Fax: 509 358 7882

Introduction

Sleep is widely found in the animal kingdom but scientists still do not know why animals sleep. One clue is that in diverse animal species, sleep loss impairs higher central nervous system functions that depend on synaptic plasticity [1]. This suggests that an evolutionarily conserved function of sleep is to promote synaptic plasticity. If true, this raises several puzzling questions. Plastic changes occur while we are awake and asleep and it is reasonable to assume that both brain states normally work in concert to produce adaptive changes in brain circuits. Sleep and wakefulness, however, are profoundly different brain states. They differ not only in their sources of activity (extrinsic inputs vs. endogenous intrinsic activation), but also in terms of single-cell and network activity, gene transcription and translation, and neuromodulator release. It seems unlikely that these brain states operate exactly the same way. It is instead probable that sleep and wakefulness operate through complementary but different mechanisms. Therefore, two important challenges are to identify how plasticity mechanisms are divided across the sleep-wake cycle and how plastic modifications initiated during one state influence plasticity in the other.

Raven et al.,[2] take a new look at the problem by comprehensively and objectively reviewing the evidence that sleep alters the morphology of synapses or the structures in neurons that contain synapses (dendritic spines). This is also known as structural plasticity. Many forms of experience-dependent plasticity are associated with structural

changes and it is believed that structural plasticity mediates persistent changes in synaptic strength. Although the discussion is wide-ranging, special emphasis is placed on plasticity within the hippocampus. This is logical as the hippocampus is a highly plastic brain structure involved in many forms of memory. The use of such a canonical model is extremely powerful, as the ways to measure synaptic plasticity in the hippocampus and the behavioral designs used to probe this structure have been continuously refined over decades. Raven et al.[2], show how combining this approach with a methodical, systematic dissection of the underlying cellular signaling pathways provides some of the strongest evidence that sleep plays a central role in synaptic plasticity. What emerges from this analysis is that sleep engages several enzymatic cascades that, in part, converge on the promotion of mRNA translation. These findings extend to the cerebral cortex suggesting that the synthesis of synaptic proteins necessary for structural plasticity may be a core function of sleep.

The authors also make important insights that agree well with other reviews of this topic [3-9]. The first is that sleep does not have one simple overall effect on synaptic strength or morphology. Sleep may reduce synapse number and strength *or* increase synapse number or strength depending on several factors. These include the brain region and circuit under examination and the type of experience that precedes sleep. Even the way animals are kept awake may lead to different synaptic changes observed after sleep. Studies that employ novel objects, or other forms of plasticity-inducing stimuli to maintain wakefulness trigger enzymatic cascades in the hippocampus that would not otherwise occur in an animal kept awake by other means. This provides a second and

important insight. Because sleep does not always lead to synaptic weakening, this raises questions about a popular theory of sleep function (the synaptic homeostasis hypothesis: SHY)

The central tenet of SHY is that sleep globally weakens synapses to offset global synaptic strengthening that occurs during wakefulness [10-12]. There have been subtle modifications to SHY over the years, evident in the different names for the process involved ('downscaling', 'synaptic renormalization' and more recently, 'selective down selection' [10-12]). Nevertheless, the central tenet has been retained. The main effect of sleep should *not* be the creation of new excitatory synapses or increases in excitatory synaptic strength. However, as reviewed by Raven et al.,[2] and others [3-7], it appears that sleep can promote new synapse formation or synaptic strengthening. These findings are based on electrophysiological, molecular and morphological measurements comparable (or similar) to those cited in support of SHY, but they cannot easily be reconciled with SHY [8, 13, 14]. Raven et al.,[2] thus provide the *coda* to what has been the *imbroglio* concerning SHY. Scientists should now move from a debate over whether all (or most of) the effects of sleep on plasticity can be explained by synaptic weakening to a discussion of how sleep leads to more complex synaptic changes.

Brain state-dependent synaptic tagging and capture

Part of the answer may reside in a variant of the *synaptic tagging and capture hypothesis* (STC) [15-17]. According to the STC, stimuli that induce synaptic plasticity set 'tags' at remodeling synapses. This process marks synapses according to their activation history (*i.e.* weak or strong) and allows for the capture of plastic related products (PRPs) driven by a later occurring, re-activation of the surrounding neuronal network [17]. An important aspect of the STC is that synaptic tags may be positive or negative. Positive tags lead to synapse strengthening or synaptogenesis, while negative (or 'inverse') tags promote synaptic weakening. This requires the capture of different PRPs at tagged synapses. For example, the immediate early genes *arc* and *homer1a* may act as negative PRPs that when translated into proteins result in synaptic weakening [18, 19]. The α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor *glur1* subunit, protein kinase M zeta (PKMζ) and possibly the brain-derived neurotrophic factor (*bdnf)* may act as positive PRPs that promote synaptic strengthening [17, 20].

Waking may be the preferred state for synaptic tagging and the synthesis of PRPs. Tags are set during waking experience [17] and many PRPs are immediate early genes (or other mRNAs) that are preferentially transcribed during waking [21, 22]. It is likely that positive and negative tags are set during wakefulness because different types of experience engage complex multi-directional changes in synaptic strength (see [4] for discussion). Sleep appears to be the preferred state for the translation of synaptic mRNAs (including PRPs) into active proteins (as discussed by Raven et al.,[2] and others [23]). The subsequent capture and translation of these PRPs during sleep can

then lead to synaptic weakening *or* strengthening in different circuits. Therefore, a *state-dependent* STC may parsimoniously explain why the effects of sleep on plasticity vary depending on the circuit and the type of experience that precedes sleep. It also provides a mechanism for linking plastic changes in one state (wakefulness) with another (sleep).

The developing visual cortex provides one possible example of state-dependent STC. Monocular deprivation during a critical period of development triggers synaptic weakening and strengthening in different visual circuits; a process known as ocular dominance plasticity (ODP) [24-26]. ODP is consolidated during sleep [27] and requires the protein kinase calcium-calmodulin kinase type II (CaMKII) [28]. Phosphorylated CaMKII may act as a positive tag as it accumulates in more activated synapses and deletion or mutation of CaMKII inhibits long-term synaptic potentiation. This may involve the synaptic sequestration of *bdnf* or other positive PRPs that form a complex with NMDA and AMPA receptors. Intriguingly, non-phosphorylated CaMKII may act as a negative tag, as it has been shown to sequester *arc* in less-activated synapses [29, 30]. Consistent with this idea following monocular deprivation, phosphorylated and non-phosphorylated forms of CaMKII are expressed in different visual synapses [31]. In addition, the positive and negative PRPs *bdnf* and *arc* are transcribed in the visual cortex during the waking induction of ODP and then translated into proteins during sleep [32]; a process required for sleep-dependent consolidation of ODP [32, 33]. These findings suggest that state-dependent STC may operate in a classic, physiological model of experience-dependent plasticity *in vivo.*

In conclusion, Raven et al.,[2] show the power of mechanism-based approaches that leverage well-established models of brain plasticity to understand sleep function. This is a strategy that does not require grand theory, just good methodical empiricism combined with precise and falsifiable hypotheses. When the results of this strategy do not fit current theories of sleep function, then it is time to consider new ideas.

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