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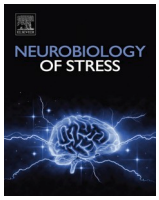

Remembering and forgetting in sleep: Selective synaptic plasticity during sleep driven by scaling factors Homer1a and Arc

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ABSTRACT

Sleep is a conserved and essential process that supports learning and memory. Synapses are a major target of sleep function and a locus of sleep need. Evidence in the literature suggests that the need for sleep has a cellular or microcircuit level basis, and that sleep need can accumulate within localized brain regions as a function of waking activity. Activation of sleep promoting kinases and accumulation of synaptic phosphorylation was recently shown to be part of the molecular basis for the localized sleep need. A prominent hypothesis in the field suggests that some benefits of sleep are mediated by a broad but selective weakening, or scaling-down, of synaptic strength during sleep in order to offset increased excitability from synaptic potentiation during wake. The literature also shows that synapses can be strengthened during sleep, raising the question of what molecular mechanisms may allow for selection of synaptic plasticity types during sleep. Here I describe mechanisms of action of the scaling factors Arc and Homer1a in selective plasticity and links with sleep need. Arc and Homer1a are induced in neurons in response to waking neuronal activity and accumulate with time spent awake. I suggest that during sleep, Arc and Homer1a drive broad weakening of synapses through homeostatic scaling-down, but in a manner that is sensitive to the plasticity history of individual synapses, based on patterned phosphorylation of synaptic proteins. Therefore, Arc and Homer1a may offer insights into the intricate links between a cellular basis of sleep need and memory consolidation during sleep.

1. Introduction

Sleep is increasingly being appreciated as a fundamental pillar of human and animal health. While the physiological function(s) of sleep remains to be fully determined, it is clear that sleep plays a critical role in maintaining brain health and cognitive functions (Diekelmann and Born, 2010; Frank and Heller, 2019; Tononi and Cirelli, 2014). In particular, memory consolidation is highly sleep sensitive (Diekelmann and Born, 2010). While the executive switching between wake and sleep states is known to be controlled by dedicated populations of wake and sleep-promoting neurons (Scammell et al., 2017), the restorative benefits of sleep are likely to be distributed throughout the brain, across circuits and cell types. Abundant evidence has shown that neuronal synapses in the mammalian forebrain are modified during sleep, suggesting that synapses are at least one major target for sleep function, and a locus of sleep need (Tononi and Cirelli, 2014; Bruning et al., 2019; de Vivo et al., 2017; Diering et al., 2017; Noya et al., 2019; Wang et al., 2018). Indeed, it is widely believed that changes in synaptic strength form the basis of information encoding in the brain and that synapses are at least one major component for memory storage (Lisman et al., 2018; Poo et al., 2016). This leads to a model where synapses are modified by experience-dependent plasticity during waking life for initial information encoding, followed by further modifications and synaptic plasticity during sleep for consolidation into long-term memory (Diekelmann and Born, 2010), or forgetting.

Not all waking experiences are consolidated into long-term memory, this is commonly called forgetting. In fact, it can be reasonably stated that the majority of daily experiences are not consolidated for long-term storage (this is true for this author at least). Far from being a passive process, forgetting may actually be an active component of the benefits of sleep, and paradoxically an essential step in the consolidation of spared memories. In the unconscious state, the brain may be able to sort waking experiences and select specific memory traces, or engrams, for consolidation, while selecting others for forgetting. Some models suggest that forgetting is actually a critical step in the consolidation of spared memories, by enhancing signal to noise (Tononi and Cirelli,

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2014; Nere et al., 2013; Poe, 2017; Kim et al., 2019). Furthermore, forgetting may be essential in renewing the brain's ability for new learning in subsequent episodes of wake, by liberating "space" for new memories to be encoded (Yoo et al., 2007; Norimoto et al., 2018). A major challenge in the field therefore, is to understand how experiences encoded during wake, and the synapses underlying them, are selected during sleep to promote either consolidation or forgetting.

In this article I will explore possible molecular mechanisms that link experience-dependent information encoding during wake, with subsequent selective modifications of forebrain excitatory/glutamatergic synapses during sleep to promote either consolidation or forgetting. This article will focus primarily on the immediate early genes Arc and Homer1a, and their described functions at excitatory post-synapses. Both of these gene products are known to be expressed in neurons in response to numerous physiologically relevant stimuli including learning, to play key roles in synaptic plasticity, and have clear links with sleep need.

2. Hebbian and homeostatic plasticity, and the synaptic homeostasis hypothesis (SHY) of sleep

Synapses of the central nervous system can change in strength in a process called synaptic plasticity. These changes can occur locally at individual synapses in an input-specific manner during long-term potentiation (LTP) or depression (LTD), collectively referred to as "Hebbian" plasticity. Hebbian plasticity is a fundamental mechanism for information coding in the brain and forms part of the molecular and cellular basis of learning and memory (Poo et al., 2016; Huganir and Nicoll, 2013; Diering and Huganir, 2018). However, neurons must maintain their overall synaptic strength within an optimal range to regulate overall excitability of neuronal circuits. Synapses can also be modified globally during homeostatic scaling in an input-independent manner (Turrigiano, 2008; O'Brien et al., 1998; Turrigiano et al., 1998). Homeostatic plasticity increases (scaling-up) or decreases (scaling-down) the strength of all synapses on a neuron, adjusting neuronal firing rates while maintaining relative synaptic strength to protect information coding from prior Hebbian plasticity events. In controlled experimental conditions, for example in primary cultured neurons, it has been possible to induce a single type of Hebbian or homeostatic plasticity in neurons for examination. However it is plausible that multiple types of plasticity have the ability to co-occur in a coordinated manner (Royer and Pare, 2003). At excitatory synapses, a fundamental mechanism to control synaptic strength in both Hebbian and homeostatic plasticity is through the regulation of the abundance of post-synaptic AMPA-type glutamate receptors (AMPARs) (Huganir and Nicoll, 2013; Diering and Huganir, 2018; O'Brien et al., 1998; Diering et al., 2014). Indeed, these plasticity types share many overlapping molecular mechanisms (Diering and Huganir, 2018). Because the molecular basis for the expression of Hebbian and homeostatic plasticity overlap, at least at the level of the post-synaptic AMPARs, these different plasticity types cannot occur completely independently, but must have dedicated mechanisms that allow for their coexistence (Diering and Huganir, 2018; Royer and Pare, 2003; Turrigiano, 2017). Moreover, emerging results show that treatments that prevent scaling-down can promote generalization of aversive memory (Diering et al., 2017; Wu et al., 2021), suggesting that Hebbian and homeostatic plasticity types both contribute to memory consolidation.

The synaptic homeostasis hypothesis (SHY) of sleep, first developed by Drs. Chiara Cirelli and Giulio Tononi (Tononi and Cirelli, 2003), posits that waking experiences are first encoded in the brain as short term memory, primarily through experience-dependent LTP (strengthening), and synapse strength is then restored to baseline by a global, but selective scaling-down of synapses (weakening) during sleep (Tononi and Cirelli, 2014). SHY offers a synapse-based mechanism to describe how sleep can promote memory consolidation and promote new learning. Specific synapses are potentiated by Hebbian LTP during wake, forming part of a memory engram. Over extended periods of wake continued information encoding through LTP results in a net increase in synaptic strength and excitability in the cortex. This process eventually leads to saturation of a neuron's ability to express LTP, thus exhausting our ability for continued learning (Yoo et al., 2007). Sleep deprivation (non-physiological extended wakefulness) has also been shown to suppress the brain's ability to express LTP (Vecsey et al., 2009). During sleep, the SHY model suggests that synapses undergo a broad weakening through non-Hebbian homeostatic plasticity, but selected engram-associated synapses are spared from this weakening or further potentiated, enabling memory consolidation through an enhancement of signal-to-noise. By restoring synapse strength to baseline, this process will also renew our ability for new learning, by desaturation of synaptic strength allowing for further information encoding through LTP in the subsequent wake period. This broad weakening of synapses may also actively contribute to forgetting. Whether synapses are weakened through scaling-down, or strengthened by LTP during sleep has been debated (Frank and Heller, 2019), and experimental evidence has been gathered to support both. It is conceivable that homeostatic scaling-down may promote a broad weakening of excitatory synapses during sleep, while at the same time selective neuronal pathways are strengthened through Hebbian LTP, or otherwise undergo a relative increase in strength by escaping the broad scaling-down process. A major question therefore, is what molecular mechanisms may allow for the selective escape, or strengthening of synapses, during a broad homeostatic weakening of synapses during sleep? The action of scaling factors Homer1a and Arc may offer some clues to this process.

3. Controversies in the field

Whether synapses become strengthened or weakened during sleep has been a topic of controversy, with compelling evidence for the occurrence of both. It is highly probable that the restorative benefits of sleep are mediated by the coordination of multiple plasticity types (Renouard et al., 2022). The reader is recommended to excellent recent studies and reviews on plasticity types expressed during sleep including mechanisms of plasticity selection (Frank and Heller, 2019; Miyamoto et al., 2021; Cary and Turrigiano, 2021; Ode and Ueda, 2020; Seibt and Frank, 2019). Another important consideration is that sleep may have very different effects on synapses in development and in adulthood. Sleep amount and architecture are highly dynamic during development (Roffwarg et al., 1966). Likewise, the density of synapses undergoes dramatic developmental changes, with profound synaptogenesis in early life, followed by a period of activity-dependent synapse pruning and elimination through the remainder of childhood and adolescence. Upon reaching adulthood, synapse density remains largely stable for the remainder of healthy life (Penzes et al., 2011). During the critical period, consolidation of ocular dominance plasticity was definitively shown to require LTP during sleep (Aton et al., 2009). During the synapse pruning phase, cortical synapse elimination has been shown to occur primarily during sleep (Maret et al., 2011). Moreover, rapid eye movement (REM) sleep in juvenile mice has been shown to be required both for the pruning of synapses and for the maturation and potentiation of spared synapses in the cortex (Li et al., 2017). Thus, during development, sleep may be important in the selective elimination and formation/maturation of synapses. It is possible that discrepant findings in this field may find some resolution when re-examined in the context of development. The role of sleep in synapse and brain development, and links with neurodevelopmental disorders, have been covered in recent review articles (Wintler et al., 2020; Doldur-Balli et al., 2022). In adults, where synapse density is stable, and plasticity is primarily occurring on pre-existing synapses (Zhang et al., 2015a), selective down-scaling of synapses may be required to maintain and refresh the plasticity of pre-existing synapses (Tononi and Cirelli, 2014). This review article will focus on putative molecular mechanisms engaged during sleep for the selection of down-scaling or potentiation of synapses in the adult cortex.

4. Synapses as a locus for sleep need

Sleep behavior is believed to be under the control of two major mechanisms, the circadian rhythm that promotes sleep at the ecologically appropriate time of day, and the homeostatic sleep drive, that promotes sleep in response to time spent awake (Frank and Heller, 2019; Borbely, 1982; Daan et al., 1984). In contrast to the circadian rhythm, the molecular and cellular basis for the homeostatic sleep drive is poorly understood. Existing literature suggests that sleep need is not localized to a few wake/sleep promoting brain regions but is actually distributed across much of the brain. In a recent set of studies, it was shown that forebrain synapses, biochemically isolated throughout the day, undergo robust daily rhythms in their transcriptome, proteome, and phosphoproteome (Bruning et al., 2019; Noya et al., 2019). Many neuronal mRNA transcripts are not translated in the cell body but are delivered to neuronal processes for local translation. Interestingly, two-thirds of synapse localized mRNAs undergo robust daily oscillations that were found to be dominated by the circadian rhythm, and largely independent of wake/sleep status (Noya et al., 2019). In contrast, oscillations in the synapse proteome and phosphoproteome were found to be largely independent of circadian mechanisms and are instead driven by wake/sleep experience (Bruning et al., 2019; Noya et al., 2019). These findings show that synapses are a nexus of interaction between sleep/-wake cycles and the circadian rhythm. The circadian rhythm allows for neurons to anticipate the needs of synapses in the coming phase, by promoting the traffic of certain RNA species to neuronal processes. Whereas modifications of the synapse proteome and phosphoproteome are a function of real-time experience and wake/sleep states. Accumulation of protein phosphorylation, particularly of certain synaptic proteins, was also recently shown to increase in response to time spent awake (Wang et al., 2018), building on the recent discovery of sleep promoting kinases, and leading to a "phosphorylation hypothesis of sleep" (Ode and Ueda, 2020; Tone et al., 2022; Funato et al., 2016; Tatsuki et al., 2016). These studies further support the notion that synapses are a locus of sleep need, and a target of sleep function.

The most established physiological marker of sleep need is the increase slow-wave activity (SWA) during non-rapid eye movement (NREM) sleep (Frank and Heller, 2019). SWA is brain activity in the delta frequency range: 0.5–4 Hz measured in the cortical electroencephalogram (EEG) (Dijk et al., 1990a, 1990b; Bjorness et al., 2009). At the cellular level, cortical SWA is generated by synchronized patterns of hyperpolarization (down-states) and depolarization (up-states) among cortical neurons (Steriade et al., 1993). The greater the voltage-oscillations and the greater the synchronization among neighboring neurons, the greater the SWA becomes. Periods of wake drive higher levels of synchrony and excitability among cortical excitatory neurons, driving the increase in subsequent NREM-SWA. Cortical synchrony and excitability are then dissipated with time spent asleep (Huber et al., 2013; Vyazovskiy et al., 2009). NREM-like SWA appears to be a default mode of microcircuit activity in cortical neurons. Synchronized down/up-state like events are seen in ex vivo cortical slice preparations and even in dissociated cortical neurons in vitro when in the absence of arousal associated neuromodulators such as orexin and noradrenaline (Hinard et al., 2012; Saberi-Moghadam et al., 2018; Pava et al., 2014; Ye et al., 2022). NREM-SWA increases in response to wake are not distributed equally across the cortex, and show higher levels in cortical areas that showed higher activity in preceding wake (Huber et al., 2004). Further, a phenomenon of local sleep has been observed, where regions of cortex exhibit a localized pattern of sleep-like slow oscillation, even when the brain is in a wake state (Krueger et al., 2019). Together these observations support a hypothesis where sleep need has a cellular, or local micro-circuit level basis, where sleep need accumulates in response to activity of individual cells, or groups of cells, during periods of wake. This local accumulation of sleep need likely involves both neurons and associated astrocytes (Vyazovskiy et al., 2009; Halassa et al., 2009; Ingiosi et al., 2020). Such a cell-based locus of sleep need is attractive because the need for sleep is conserved across phyla, whereas the circuits known to control wake and sleep behavior are not broadly conserved. Indeed, sleep-like behavior and sleep homeostasis has even been demonstrated in organisms with a distributed nervous system (no brain), such as in jellyfish (Nath et al., 2017). How sleep need localized to individual synapses, cells, or micro-circuits is ultimately transmitted to sleep-promoting brain regions, such as the ventrolateral pre-optic nucleus of the hypothalamus is not known.

Mechanistically, localized accumulation of sleep need may involve the induction of immediate early genes within activated neurons (Maret et al., 2007; Mackiewicz et al., 2008; Suzuki et al., 2020), the accumulation of phosphorylations on sleep-sensitive synaptic proteins (Wang et al., 2018; Ode and Ueda, 2020), Ca^{++} signaling in astrocytes and the accumulation of sleep promoting metabolites such as extracellular adenosine (Bjorness et al., 2009, 2016; Halassa et al., 2009; Ingiosi et al., 2020; Porkka-Heiskanen et al., 1997; Blum et al., 2021). Each of these mechanisms can act in a local manner and as a function of waking activity. According to the synapse homeostasis hypothesis of sleep, broad but selective weakening of excitatory synapses during sleep is needed to offset the strengthening of synapses through LTP during wake. Accordingly, the cellular accumulation of sleep need should be directly related to LTP-type plasticity during wake, and should be localized to the individual cells that are engaged in learning. LTP-inducing stimuli are known to drive the expression of a constellation of gene products collectively referred to as immediate early genes (IEGs) (Demmer et al., 1993; Saha and Dudek, 2013; Lanahan and Worley, 1998). These IEGs include Arc and Homer1a whose expression is also potently induced by sleep deprivation (Maret et al., 2007; Suzuki et al., 2020). Indeed, Homer1a mRNA has even earned the nickname "the molecular marker of sleep need". Arc is not required for the induction of LTP (Kyrke-Smith et al., 2021), and overexpression of Homer1a can suppress LTP (Rozov et al., 2012; Celikel et al., 2007), but both are required for homeostatic scaling-down in cultured cortical neurons (Hu et al., 2010; Shepherd et al., 2006) and for the remodeling of synapses during sleep (Diering et al., 2017; Suzuki et al., 2020), suggesting that the induction of LTP simultaneously initiates a program of homeostatic plasticity. Therefore, individual cells that are heavily engaged in learning during wake will also have a net increase in synaptic strength resulting from LTP, and these same cells will be the primary beneficiaries of synaptic renormalization during sleep through Arc/Homer1a dependent homeostatic scaling-down. Cells that were not engaged in plasticity during wake, and that have no induction of Arc and Homer1a, may express less "sleep need" and will not require synaptic renormalization. Thus, localized sleep need may be a function of the accumulation of scaling factors including Arc and Homer1a, serving as a mechanism to link learning, sleep need and synaptic renormalization during sleep in a cell based manner (Fig. 1 – panel 1).

5. Gating of synaptic plasticity and consolidation by wake and sleep

Why do we need to be unconscious for sleep to perform its function (s)? Sleep and wake transitions occur rapidly over seconds to minutes. During these transitions, the brain undergoes dramatic changes in neuronal firing patterns and neuromodulatory tone (Scammell et al., 2017; Poe, 2017). It is highly plausible the types of synaptic plasticity, and the underlying molecular mechanisms, are dramatically affected by these very different brain states (Pawlak et al., 2010). For instance, the higher levels of noradrenaline during wake are known to reduce the threshold for the induction of LTP (Hu et al., 2007), and spike time dependent plasticity in cortical neurons is biased towards depression during NREM-like cortical up-states (Gonzalez-Rueda et al., 2018). Neurons face an important dilemma of plasticity vs. stability. The wake state may be optimized to favor the rapid encoding of memory through experience-dependent LTP, but at the cost of introducing instability in the excitability of neuronal networks (Vyazovskiy et al., 2009). Sleep

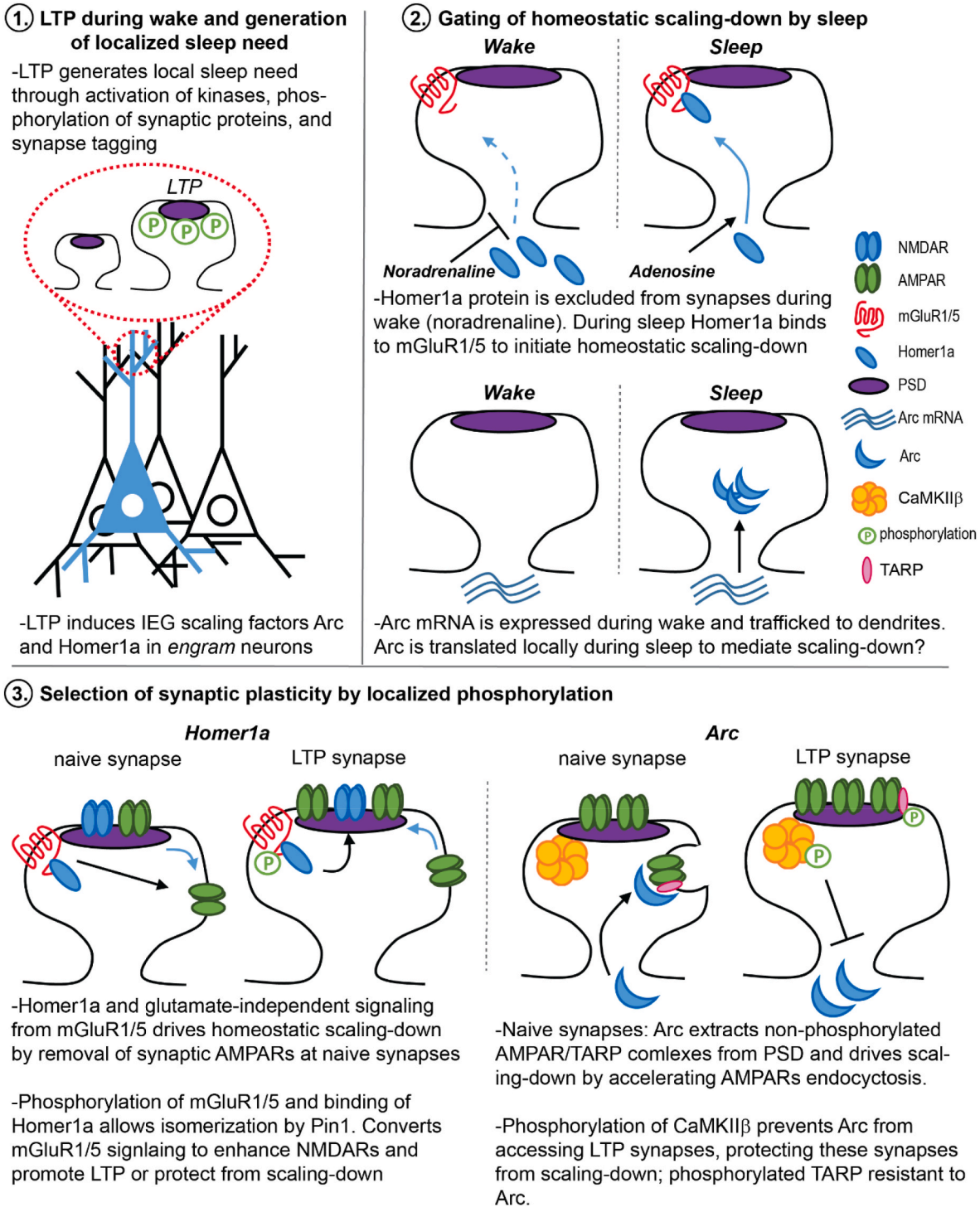

Fig. 1. Summary figure. Panel 1: experience dependent LTP during wake generates localized sleep need through induction of neuronal immediate early genes (IEGs), including scaling factors Homer1a and Arc, and through activation of sleep promoting kinases and phosphorylation at engram synapses. Panel 2: homeostatic scaling-down driven by Homer1a and Arc is gated by the transition from wake to sleep. Panel 3: potential mechanisms for synapse selection allowing for engram synapses to escape from broad scaling-down, or for further potentiation.

may provide conditions favoring certain homeostatic forms of plasticity such as scaling-down, perhaps at the cost of limiting, but not removing, the capacity for expression of Hebbian plasticity.

Changes in neuronal firing rate are often used to infer changes in excitatory synaptic strength. Recent work has shown that homeostatic regulation of neuronal firing rate in the visual cortex is highly sensitive to the wake sleep cycle. Eyelid suture (visual deprivation) results in an immediate decrease in neuronal activity in the visual cortex corresponding to the deprived eye. Over several days, homeostatic mechanisms are engaged to increase neuronal excitability and restore neuronal firing rates back to their original set-points. By combining neuronal firing rate measurements with analysis of wake/sleep states it was found that the homeostatic increase in firing rate in response to visual deprivation occurred only during wake, and was blocked by sleep (Hengen et al., 2016). In contrast, when the eyelid suture is removed, restoring visual input, the neurons in the visual cortex experience a large

increase in their firing rates, as visual input is now acting on a circuit with increased excitability (Torrado Pacheco et al., 2021). In this situation, neuronal firing rates are gradually reduced over days, through a homeostatic suppressing of neuronal excitability, again to restore firing rates to an original set-point. Importantly, this homeostatic weakening of excitability selectively occurs during sleep, and is blocked by wake (Torrado Pacheco et al., 2021). Together, these studies show clearly that wake and sleep form permissive states for, or perhaps gate, certain forms of plasticity. This then raises the question of what molecular mechanisms underlie the promotion of different plasticity types through the wake-sleep cycle?

6. Synaptic tag and capture and plasticity selection during sleep

It has been long known that de novo protein synthesis is generally required to maintain long-lasting Hebbian plasticity in ex vivo preparations, and also to consolidate newly encoded memories (Davis and Squire, 1984). The new proteins needed to consolidate plasticity and memory are referred to as plasticity related products (PRPs). The synaptic tag and capture (STC) model offers an attractive framework to describe how the necessary PRPs are recruited to the engram associated synapses. During the induction phase of Hebbian plasticity, a temporary "tag" is created in association with the modified synapses that allows for the selective recruitment of the necessary PRPs (Fig. 1 - panel 1). If PRPs are recruited while the tag remains intact the synaptic plasticity can be consolidated, whereas if the tag decays before PRPs can be recruited the synapse returns to its original state (Frey and Morris, 1997). The nature of the synaptic tag is not known; activation of certain protein kinases and an associated pattern of phosphorylation, together with a change in the structure of the actin cytoskeleton are attractive candidate mechanisms (Pinho et al., 2020; Sanhueza and Lisman, 2013; Ramachandran and Frey, 2009; Huang et al., 2006). The original STC model has since been nuanced by the additional description of "positive," "negative," and "inverse" synaptic tagging (Araki et al., 2015; Okuno et al., 2012). A provocative idea recently put forward posits that activity dependent plasticity during wake establishes a synaptic tag, priming the associated synapses for further processing, and that synthesis/recruitment of PRPs and memory consolidation occur during sleep (Seibt and Frank, 2019). Again, this hypothesis is based on the premise that vastly different brain states of wake and sleep favor or enable certain molecular mechanisms; synaptic tagging and priming during wake, protein synthesis, capture and consolidation during sleep.

While the need for new proteins in memory/plasticity consolidation is established, the identity of the required PRPs is not known. IEGs are induced in neurons in response to LTP and it is believed that some subset of these may be the necessary PRPs for consolidation. Homer1a protein (also called VESL-1S) was one of the first IEGs shown to "conform to synaptic tag and capture", in that it was found to accumulate at activated synapses following LTP induction (Okada et al., 2009). Curiously, a subset of the IEGs induced in response to LTP, including Arc and Homer1a, do not seem to be involved in synapse strengthening, but actually drive homeostatic weakening of synapses (Hu et al., 2010; Shepherd et al., 2006). Other IEGs, such as NPAS4 and NPTX2 seem to be involved in promoting feed-forward inhibition from local interneurons, reducing excitability within cortical microcircuits (Chang et al., 2010; Lin et al., 2008; Xiao et al., 2021). This suggests that synaptic potentiation during LTP also initiates a coordinated homeostatic program to reduce synapse strength and local excitability to prevent destabilization of neuronal networks and promote memory consolidation. It is possible that this homeostatic program set in motion through the experience-dependent induction of these IEGs during wake, is only engaged once the permissive sleep state is initiated (Torrado Pacheco et al., 2021) (Fig. 1 – panel 2).

The concept of synaptic tagging may also be very useful in understanding how specific synapses may undergo differential plasticity types during sleep, and may go beyond the recruitment of newly generated PRPs. A molecular tag could be generated at individual synapses during waking Hebbian plasticity events, in accordance with the STC model. If this tag endures into the subsequent sleep phase this tag may modify the susceptibility of individual synapses to homeostatic weakening, allowing for selective down-selection, or otherwise may prime these synapses for further plasticity (Fig. 1 – panel 3). Patterned or cumulative phosphorylation is an attractive mechanism that may "tag" individual synapses and signal a local accumulation of sleep need (Wang et al., 2018; Ode and Ueda, 2020). As an example, active PKA kinase is known to be localized to specific nano-domains through interaction with A-Kinase Anchoring proteins (AKAPs), such as AKAP79/150 which is localized to excitatory post-synapses (Sanderson and Dell'Acqua, 2011; Smith et al., 2017). AKAPs are one leading candidate for the basis of synaptic tagging (Huang et al., 2006). Phosphorylation of GluA1-containing AMPARs at S845 is mediated by PKA-AKAP150, and is associated with synaptic strengthening/LTP (Diering and Huganir, 2018). During homeostatic scaling-down and during sleep, synaptic AKAP150, PKA, and GluA1 phospho-S845 are decreased, suggesting that the loss of synaptic anchored PKA may favor synapse weakening (Diering et al., 2014, 2017). However, it was also found that during homeostatic scaling-down, dephosphorylated GluA1 is preferentially removed from synapses, whereas GluA1 containing receptors that maintain phosphorylation are resistant to scaling-down and remain localized to synapses (Diering et al., 2014). This vignette supports the concept that each synapse's history (LTP), as expressed by localized and patterned phosphorylation, or localized kinase activity, can influence future synaptic plasticity (scaling-down). Both Arc and Homer1a are known to drive a broad homeostatic scaling-down of synapses, but also in a manner that is sensitive to localized phosphorylation (Fig. 1 – panel 3).

7. Arc, synaptic plasticity and sleep

Activity regulated cytoskeleton associated protein, Arc, is an IEG robustly induced in neurons in response to learning related behavior or induction of Hebbian plasticity (Saha and Dudek, 2013). Arc is also robustly induced by sleep deprivation (Maret et al., 2007; Suzuki et al., 2020). Arc has numerous functions throughout the neuron, including in the nucleus, cytoplasm, synapse, and even outside the neuron. Phylogeny and structural analysis suggest that Arc has a retroviral origin (Zhang et al., 2015b). Indeed, Arc has recently been shown to form viral like particles that can bud from activated neurons and potentially transmit biological materials such as RNA to neighboring cells (Pastuzyn et al., 2018). The myriad functions of Arc throughout the neuron remain to be fully described. Here I will focus on the known effects of Arc in synaptic plasticity. Arc mRNA is induced within minutes of neuronal activity, the transcript is then known to undergo trafficking into neuronal processes where it can be translated in a localized and activity-dependent manner within dendrites and near synapses (Steward et al., 1998; Park et al., 2008). At synapses, Arc binds to the endocytic proteins Endophilin2 and Dynamin3, that collectively accelerate the endocytosis of post-synaptic AMPARs, mediating synapse weakening during homeostatic scaling-down and mGluR-LTD (Shepherd et al., 2006; Chowdhury et al., 2006; Waung et al., 2008). Under certain conditions, Arc mRNA can be induced by experience, and the accumulation of Arc mRNA in dendrites can then influence future synaptic plasticity events such as mGluR-LTD (Jakkamsetti et al., 2013).

Does Arc mediate selective down-scaling of synapses during sleep? As mentioned, Arc is rapidly induced in neurons engaged in learning and behavior, and in response to extended periods of wake. Recently Arc KO mice were shown to have blunted physiological and molecular responses to sleep deprivation, suggesting that Arc may be part of the molecular basis for sleep need (Suzuki et al., 2020). Within dendrites, Arc has been shown to drive a selective weakening of excitatory synapses based upon the phosphorylation and activity of CaMKIIβ (Okuno et al., 2012). Like CaMKIIα, CaMKIIβ undergoes auto-phosphorylation at the activation site T286/T287 (Coultrap and Bayer, 2012). Arc was shown to bind

preferentially to inactive, de-phosphorylated CaMKIIβ leading to Arc accumulation at inactive synapses, whereas Arc is excluded from active synapses that contain phosphorylated CaMKIIβ. This selective synaptic localization was described as "inverse synaptic tagging" and was demonstrated to drive a selective homeostatic weakening of inactive synapses, whereas recently activated synapses are spared from scaling-down, driving an enhancement of signal to noise (Okuno et al., 2012) (Fig. 1 – panel 3). Interestingly, CaMKIIβ was recently described as a sleep promoting kinase (Tone et al., 2022), and CaMKIIβ was also shown to accumulate phosphorylations in response to sleep deprivation, one of the so called sleep-need index phospho proteins (SNIPPs) (Wang et al., 2018; Ode and Ueda, 2020; Tatsuki et al., 2016). Another mechanism for selective plasticity by Arc protein was recently described using a purified protein reconstitution system. Prominent post-synaptic density (PSD) scaffold proteins including PSD95, Homer and Shank proteins can form liquid-liquid phase separated (LLPS) condensates that are able to co-concentrate AMPAR auxiliary subunit TARP proteins (Chen et al., 2022; Zeng et al., 2018, 2019). Purified Arc was able to selectively extract TARP proteins from PSD-like condensates only when dephosphorylated, whereas phospho-mimetic TARP was resistant to Arc (Chen et al., 2022). Therefore, Arc a is able to remove TARP-AMPAR complexes from synapses based on the phosphorylation history (LTP) of the associated synapses (Fig. 1 – panel 3).

Together, these findings lead to the following hypothetical model. Wake related activity can lead to the localized accumulation of sleep need, through increased levels of Arc mRNA and activation and phosphorylation of CaMKII kinases within "engram neurons" (Tatsuki et al., 2016; Suzuki et al., 2020) (Fig. 1 – panel 1). Active CaMKII promotes sleep behavior, but also is a major mediator of Hebbian LTP. Persistent activity of CaMKIIβ and phosphorylation of TARPs at active synapses acts to protect "engram associated synapses" from homeostatic scaling-down (Okuno et al., 2012; Chen et al., 2022). Once sleep is initiated Arc drives the selective weakening of synapses through endocytosis of AMPARs, only at inactive synapses, sparing memory associated synapses, and thus supporting memory consolidation through enhanced signal to noise (Fig. 1 – panel 3). A prediction of this model is that Arc mRNA trafficked to dendrites during wake will be translated into protein during sleep, or otherwise that the scaling-down functions of Arc are gated by the transition to sleep (Fig. 1 – panel 2). These predictions will require additional experimental validation. This model is line with a recent idea that protein synthesis/capture of plasticity related products (PRPs), should occur preferentially during sleep (Seibt and Frank, 2019).

8. Homer1a and synaptic plasticity

The Homer family consists of three genes, Homer1-3, that encode prominent scaffold proteins localized to the excitatory post-synapse. Homer1-3 forms direct interactions with Shank1-3 family scaffolds and indirect interactions with DLG1-4 (PSD95) and GKAP1-4 scaffolds, together forming a cross-linked network that makes up much of the structure of the post-synaptic density (PSD) (Zeng et al., 2018; Tu et al., 1999; Hayashi et al., 2009). This protein cross-linked scaffold network additionally recruits and anchors glutamate receptors, cytoskeletal proteins, and synaptic enzymes and signaling components adding various functions to the post-synapse. In vitro, purified PSD scaffold proteins are known to undergo liquid-liquid phase separation (LLPS) (Zeng et al., 2018). Homer1 undergoes alternative splicing to produce long and short forms isoforms. Long isoforms Homer1b/c and Homer2/3 are constitutively expressed in neurons and consist of an N-terminal Ena/VASP homology (EVH) domain and a C-terminal coiled coil domain. The Homer EVH domain binds to a consensus PPXXF motif found in proline-rich domains of interacting partners, while the coiled coil domain drives self-assembly to form tetramers (Hayashi et al., 2009; Xiao et al., 1998). This domain structure allows for long Homer to bind multiple proteins such as metabotropic glutamate receptors mGluR1/5 and inositol triphosphate receptors (IP3Rs), and cross link them to the PSD scaffold network, anchoring critical functions to the post-synapse (Tu et al., 1998). Short from Homer1a is an activity induced IEG that contains the N-terminal EVH domain only, and lacks the coiled coil needed for tetramerization and cross-linking (Brakeman et al., 1997). Therefore, Homer1a acts as a natural dominant negative protein by competing for protein binding partners shared with long-Homer, and preventing their association with the PSD scaffold network. It was recently shown that addition of purified short form Homer1a protein to PSD-like biological condensates could drive shrinkage and dispersion of these PSD-like condensates by interfering with the function of cross-linking Homer (Zeng et al., 2018). This suggests that Homer1a can have broad effects on excitatory synapses by favoring the shrinkage of the PSD. Homer1a has also been shown to act in a protective manner in neurons mitigating excitotoxic and cellular stress and suppressing apoptosis, consistent with a homeostatic function for Homer1a in limiting overall neuronal excitability (Wang et al., 2015, 2020; Wei et al., 2019; Wu et al., 2018; Fei et al., 2015).

Homer1a also has very specific effects on synaptic signaling by altering the signaling properties of group 1 metabotropic glutamate receptors mGluR1/5[115]. mGluR1/5 are broadly expressed in the excitatory post-synapse and play key roles in synaptic plasticity, including both Hebbian and homeostatic plasticity (Bockaert et al., 2021; Marton et al., 2015). Activation of mGluR1/5 with the selective agonist DHPG triggers mGluR-mediated LTD, a plasticity type that can also be induced electrically, with certain paradigms of low-frequency stimulation (Huber et al., 2001). Homer1a binding to the intracellular C-terminal of mGluR1/5 uncouples these receptors from the PSD scaffold network, and in doing so, triggers a conformational change that converts the receptor into a constitutively active state that is independent of glutamate binding (Bockaert et al., 2021; Marton et al., 2015; Ango et al., 2001). It has been shown that Homer1a induction and binding to mGluR1/5, and the glutamate-independent constitutive mGluR1/5 signaling are required for the expression of homeostatic scaling-down in cultured cortical neurons (Hu et al., 2010). Induction of Homer1a and homeostatic scaling down has been shown to limit epilepsy pathogenesis in vivo, using a pentylenetetrazol induced kindling model (Shan et al., 2018). Additionally, Homer1a and mGluR1/5 signaling have also been shown to be necessary for the broad reduction in synaptic AMPARs during sleep (Diering et al., 2017) (more below). Thus, Homer1a induction and binding acts as a molecular switch for mGluR1/5 signaling (Fig. 1 – panel 3). In the absence of Homer1a, mGluR1/5 are coupled to the PSD and participate in input-specific and glutamate dependent Hebbian plasticity, and upon Homer1a binding mGluR1/5 broadly signal across neurons indepedent of glutamate to drive homeostatic scaling-down (Marton et al., 2015).

9. Homer1a and selective synapse weakening during sleep

Homer1a has extensive links with sleep in the literature. As described above, the increase in NREM-SWA is the most widely established physiological marker of sleep need. The accumulation of NREM-SWA activity in mice as a function of wake has a strong genetic basis (Franken et al., 2001), which was found to be partly explained by polymorphisms within the Homer1 gene (Maret et al., 2007; Mackiewicz et al., 2008). These polymorphisms may regulate the extent of Homer1a induction in response to sleep deprivation. Polymorphisms in Homer1 have also been linked with sleep phenotypes in humans (Pedrazzoli et al., 2020). Selective deletion of short-form Homer1a in mice resulted in increased time in NREM sleep and an inability to sustain long periods of wake (Naidoo et al., 2012). One possible interpretation of this phenotype is that loss of Homer1a limits the restorative synaptic functions of sleep, ultimately affecting the mouse's ability to sustain wakefulness, despite a compensatory but ineffectual increase in NREM sleep. Deletion of mGluR5 in mice results in a similar phenotype with reductions in wake time and wake bout length and increased NREM sleep

(Aguilar et al., 2020; Holst et al., 2017). Deletion of the single Homer homolog in drosophila (only long-form Homer), or mutation of the homer binding site in DmGluRA (mGluR homolog) resulted in reduced sleep time and sleep fragmentation (Naidoo et al., 2012; Ly et al., 2020), showing that a link between Homer and mGluR in sleep is evolutionarily conserved.

We recently showed that Homer1a is required for the broad reduction of forebrain synaptic AMPA-type glutamate receptors during sleep (Diering et al., 2017), just as it is required for homeostatic scaling-down in cultured cortical neurons (Hu et al., 2010). Importantly, we show that even though Homer1a mRNA is expressed during wakefulness (Maret et al., 2007), Homer1a protein does not accumulate at synapses during wake, but associates with synapses during the transition to sleep. Homer1a localization to the synapse is prevented by wake-promoting noradrenaline acting through α and β-adrenoreceptors, and is promoted by sleep-promoting adenosine through A1 adenosine receptors (Diering et al., 2017). These findings support a model where Homer1a is induced in neurons by experience-dependent plasticity (LTP) during wake (Fig. 1 – panel 1), but where the induction of homeostatic scaling-down mediated by Homer1a is prevented until the transition to sleep (Fig. 1 – panel 2). During wake, mGluR1/5 receptors are coupled to the PSD through binding the long-Homer scaffold network and signal in a glutamate-dependent manner to support Hebbian plasticity events. During sleep, mGluR1/5 are disengaged from the PSD network in engram cells by binding to dominant negative Homer1a, and are converted to a glutamate-independent constitutive signaling mode driving homeostatic scaling-down (Diering et al., 2017; Hu et al., 2010; Bockaert et al., 2021; Martin et al., 2019). This work thus provides part of a molecular basis to explain how wake and sleep states may gate, or bias, certain forms of synaptic plasticity (Torrado Pacheco et al., 2021). This model is also attractive because it provides molecular links between experience-dependent plasticity during wake with the localized accumulation of sleep need in a cell autonomous fashion.

Homer1a binding to mGluR1/5 can also drive signaling that promotes LTP, conditional upon the phosphorylation of the homer-binding ligand in the mGluR1/5 C-terminus and isomerization by prolyl isomerase Pin1 (Marton et al., 2015; Park et al., 2013). mGluR1/5 can be modified through multiple phosphorylations within the intracellular regions that can regulate protein trafficking and signaling functions (Mao et al., 2008). In a recent phosphoproteomics analysis it was found that mGluR5 accumulates phosphorylations in response to sleep deprivation, one of the so called sleep need index phospho-proteins (SNIPPs) (Wang et al., 2018). Phosphorylation of the Homer binding site within the mGluR1/5 C-terminus is mediated by proline-directed kinases CDK5 or Erk1/2 acting downstream of neuromodulators (Hu et al., 2012). This phosphorylation increases the binding affinity of Homer proteins, allowing for Homer1a to compete with the constitutively expressed and more abundant long-form Homer, and also allowing for the selective accumulation of Homer1a at "activated" synapses (Okada et al., 2009; Park et al., 2013). The co-occurrence of Homer1a binding (conditional on IEG induction) and mGluR1/5 phosphorylation (conditional on neuromodulation) permits the binding of prolyl isomerase Pin1. Pin1-dependent proline isomerization of mGluR1/5 then drives an enhancement of NMDAR function that promotes LTP, and/or protects activated synapses from de-potentiation and scaling-down (Fig. 1 – panel 3).

This Homer1a/phospho-mGluR/Pin1/NMDAR mechanism was described in cortical striatal synapses in the context of reward learning but it is plausible that the same mechanism may be relevant in the cortex to mediate selective strengthening vs. weakening of cortical synapses during sleep. Here I propose a hypothetical selection mechanism. First, Homer1a is induced in neurons engaged in LTP during wake, but Homer1a protein is excluded from synapses by high noradrenaline tone. Second, mGluR1/5 are phosphorylated at specific (engram) synapses by CDK5 or Erk1/2. Third, upon entering the sleep state the decline in noradrenaline tone permits Homer1a targeting to synapses where it binds to mGluR1/5 and initiates a signaling state that drives synaptic plasticity. In most synapses (naïve synapses), Homer1a-mGluR1/5 drives a broad weakening of synapses through homeostatic scaling-down. At engram associated synapses that contain phosphorylated mGluR1/5, Homer1a-mGluR1/5 enhances NMDAR function that protects these synapses from scaling-down and promotes LTP (Fig. 1 – panel 3). Thus, similar to the description of Arc above, Homer1a induced signaling may mediate part of the restorative benefits of sleep through homeostatic weakening of synapses to reduce neuronal excitability, but in a manner that is sensitive to the prior history (LTP) of individual synapses.

10. Future directions

In order to support cognitive functions such as the renewal of learning and consolidation of memory, it is believed that synapses are at least one major target of sleep function. The discovery of sleep promoting kinases and the wake-dependent accumulation of phosphorylations, largely on synaptic proteins further support synapses as a locus of sleep need and target of sleep function. Sleep need is not localized to specific sleep promoting neurons but is distributed across the brain in proportion to waking neuronal activity, and likely has a cellular or micro-circuit basis that involves both neurons and associated glia. One leading hypothesis on the benefits of sleep, at least in adults, is that sleep will drive a broad but selective weakening of synapses to offset the excitability increase driven by Hebbian LTP that encodes experiences from wake (Tononi and Cirelli, 2014). Therefore, the localized accumulation of sleep need should be directly related to experience dependent LTP during wake. However, compelling evidence in the literature also suggests that consolidation of synaptic plasticity during sleep involves multiple synaptic plasticity types. This raises the question of how synapses can be selectively modified during sleep to restore neuronal excitability and consolidate memory engrams. The role of forgetting in memory consolidation is often "forgotten". Forgetting may in fact be an active and selective process that occurs during sleep that is critical for the consolidation of selected memory traces. Here, I propose that the activity-induced scaling factors Arc and Homer1a provide mechanistic insights into the localized accumulation of sleep need within specific neurons, and the selective synaptic plasticity that occurs during sleep. These mechanisms may also offer insights into the processes of forgetting. More work will be needed to understand how selective plasticity during sleep informs the processes of memory consolidation and forgetting.

11. NREM and REM

Why are there two very different sleep states? The particular functions of each sleep state are far from understood, but it is very likely that the two states have important interactions related to synaptic plasticity. It is likely that the very different patterns of neuronal activity known to occur during NREM and REM will bias or gate certain types of plasticity. Selective scaling-down has been proposed to occur primarily during NREM (Tononi and Cirelli, 2014). Here I suggest that the selective down-scaling via Homer1a and Arc are influenced by synaptic tagging during wake, specifically patterned phosphorylations at the single synapse level by CaMKIIβ and Erk1/2 or CDK5 (Okuno et al., 2012; Park et al., 2013). One possibility is that wake-like patterns of neuronal activity during REM are needed to renew or maintain these synaptic tags first established during wake, thus protecting memory engrams from scaling-down during subsequent rounds of NREM. Another possibility is that synapses that escape from scaling down during NREM can then undergo further Hebbian-type plasticity (LTP) during REM, to further enhance signal to noise and integrate newly formed memories with pre-existing schemas. This could be achieved by synaptic and dendritic calcium spikes that can been observed during REM sleep but not NREM (Li et al., 2017).

12. Circadian rhythms and synaptic plasticity

Just as the wake and sleep states may gate, or otherwise bias certain types of plasticity, the circadian rhythm may also bias certain synaptic processes in a time of day dependent manner. Recent work on the rhythms of the synaptic transcriptome, proteome, and phosphoproteome show that synapses are a nexus of interaction between sleep and circadian rhythms. Interestingly, Homer1a transcription is known to have a robust circadian expression pattern as well as a clear induction in response to sleep deprivation. A recent study has shown that Homer1a transcription is under the control of BMAL1 and CREB proteins, well known players in circadian rhythms and activity-dependent gene expression respectively (Sato et al., 2020). Surprisingly, circadian regulation of Homer1a transcripts is intact in the BMAL knock out mice, but the induction of Homer1a in response to SD is completely blunted. This suggests that BMAL, a very well characterized component of the molecular clock, is needed to prime the Homer1a promoter to respond to SD, likely in a circadian manner (Sato et al., 2020). In other words, the circadian clock may prepare the brain to respond to SD during the sleep phase. Thus, the mechanisms described here are very likely to be influenced in important ways by the circadian rhythm. Clearly more work is needed to fully understand the intricate interactions between the wake sleep cycle and circadian rhythms as they relate to synaptic plasticity and learning and memory.

12.1. Inhibitory synapses

This review article primarily describes relevant mechanisms of excitatory post-synaptic plasticity, the known cite of action of scaling-factors Arc and Homer1a. Inhibitory GABAergic synapses have also been described to undergo long-lasting plasticity including long lasting potentiation (iLTP). The role of the sleep-wake cycle in the processes of inhibitory synapses plasticity are poorly understood. A recent study provides some of the first description for differential expression of iLTP during the wake sleep cycle (Wu et al., 2022), suggesting the differential plasticity of inhibitory synapses may also contribute to information processing and memory consolidation during the sleep wake cycle. Clearly, more work is needed to characterize the inhibitory synapse plasticity types engaged during sleep and their functions in learning and memory. It is highly likely that coordinated mechanisms are engaged at both excitatory and inhibitory synapses during sleep to promote memory consolidation, or forgetting. Perhaps some of the principles described here for plasticity-selection by Arc and Homer1a at excitatory synapses may similarly apply to plasticity factors active at inhibitory synapses.

13. Conclusion

The mechanisms involving Arc and Homer1a described here are able to link several important observations and ideas in the field. Neurons engaged in learning during wake will also express the IEG scaling factors Arc and Homer1a directly in proportion to the level of LTP engaged, and thus these will be the neurons to benefit from the restorative synapse renormalization during sleep. This matches observations that polymorphisms in Homer1a partly explain the genetic basis for the accumulation of sleep need measured by NREM-SWA (Maret et al., 2007; Mackiewicz et al., 2008). Activation of sleep promoting kinases such as CaMKIIβ and Erk1/2 are also linked with neuronal activity, and can therefore also form part of the basis for localized accumulation of sleep need (Ode and Ueda, 2020; Tone et al., 2022). Specific patterns of phosphorylation generated by these kinases at individual synapses can then influence the susceptibility of each synapse to scaling-down driven by Arc and Homer1a, providing synapse-level specificity that can promote enhanced signal to noise. This idea also builds on the previous model of synaptic tag and capture (STC), where Hebbian plasticity, during wake, initiates a tag that controls how these synapses will be modified in future. This also suggests that localized sleep need may even extend to the individual synapse level. Finally, the mechanisms described here rely on observations that certain plasticity types will be gated by the vastly different patterns of neuronal activity and neuromodulatory tone between wake and sleep (Poe, 2017). Gating of plasticity through Homer1a is partly explained by the exclusion of Homer1a protein from synapses when wake associated noradrenaline is high. Gating of plasticity by Arc could be explained by a localized translation of Arc during sleep. This will require experimental validation, but is in line with recent thinking in the field (Seibt and Frank, 2019).

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Declaration of competing interest

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