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REVIEW

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Homer1a and mGluR1/5 Signaling in Homeostatic Sleep Drive and Output

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Sleep is an essential physiological behavior that promotes cognitive development and function. Although the switch between sleep/wake cycles is controlled by specific neural circuits, sleep need and the restorative benefits of sleep are likely controlled by cellular mechanisms localized in critical areas of the brain involved in learning and memory including the cortex and hippocampus. However, the molecular basis for the restorative function(s) of sleep that support cognition, or for the homeostatic build-up of sleep need are poorly understood. Synapses undergo local and global changes in strength to support learning and memory and are likely a point of restoration during sleep. Homer1a and mGluR1/5, recently implicated in sleep function, are molecules involved in the scaling down process that weakens synapses during sleep to restore synapse homeostasis. During wake, long-form Homer proteins tether mGluR1/5 to IP3R and to the post-synaptic density (PSD†). During sleep, short-form Homer1a uncouples mGluR1/5 from IP3R leaving mGluR1/5 open to interact with other effectors, switching mGluR1/5 signaling from "awake-type" to "sleep-type" signaling modes. Importantly, mGluR1/5 have been implicated in several neurological and neurodevelopmental disorders such as Alzheimer's disease (AD) and autism spectrum disorder (ASD), all of which show abnormal sleep phenotypes, linking sleep, disease, and mGluR1/5 signaling. Further investigation into the downstream effectors of mGluR1/5 and sleep/wake signaling will lead to more targeted therapeutic interventions.

INTRODUCTION

Sleep is an essential conserved behavior that supports higher cognitive functions including attention, working memory, emotional control, and learning and memory [1]. Sleep is controlled by both circadian and homeostatic processes such that sleep is promoted at the ecologically appropriate time of day, and sleep need increases

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†Abbreviations: AMPARs, AMPA-type glutamate receptor; AD, Alzheimer's disease; ASD, autism spectrum disorder; CFC, contextual fear conditioning; GPCR, G-protein coupled receptor; EVH, ena vasp homology; IP3R, inositol triphosphate receptor; LTD, long-term depression; LTP, long-term potentiation; MAP kinase, mitogen activated protein kinase; mGluR1/5, metabotropic glutamate receptor 1/5; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin; NAM, negative allosteric modulator; NREM, non-rapid-eye-movement; PAM, positive allosteric modulator; PET, positron emission tomography; PKC, protein kinase C; PSD, post-synaptic density; REM, rapid-eye-movement; SAM, silent allosteric modulator; SD, sleep deprivation; SHY, synapse homeostasis hypothesis; SWA, slow-wave activity.

Keywords: sleep, synapse, synaptic plasticity, memory, glutamate receptors, immediate early gene, Alzheimer's disease, autism

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with time spent awake and active [1,2]. The molecules that control the circadian clock have been well described, as has the role of the central clock (the suprachiasmatic nucleus), in coordinating rhythmic behavior in mammals [3]. In addition, the brain circuits controlling wake and sleep in mammals are under intense investigation and several wake and sleep centers have been described [4]. These wake/sleep control centers are primarily clustered in the "ancient" brain within the midbrain, particularly in the hypothalamus, and are likely to be well conserved [4]. While the executive switching between wake and sleep states is controlled by discrete neural circuits, the restorative "output" of sleep that supports cognitive functions, likely involves many or all brain regions including the hippocampus and cortex [5]. Likewise, the homeostatic buildup of sleep need is likely distributed throughout the brain and may have a cellular rather than a circuit basis [5]. This distributed homeostatic build-up of sleep need would allow separate brain regions to benefit from sleep based on prior waking experience. Acute sleep disruption has immediate measurable consequences on cognitive function, which become increasingly affected by chronic sleep disruption [1]. Chronic sleep disruption also has implications for immune function and metabolism. Sleep disruption is associated with many neurological and psychiatric diseases including Alzheimer's disease (AD), autism spectrum disorder (ASD), and others, suggesting that therapeutics designed to improve sleep may be broadly effective in a range of conditions [6,7]. The molecular basis for the restorative function(s) of sleep that support cognition, or for the homeostatic build-up of sleep need are poorly understood. Here we review recent literature implicating the type 1 metabotropic glutamate receptors (mGluR1/5) and the immediate early gene Homer1a in the build-up of sleep need and the restorative processes of sleep.

SLEEP AND SYNAPTIC PLASTICITY

Synapses in the central nervous system undergo bidirectional changes in synaptic strength, a process referred to as synaptic plasticity. These changes occur locally at individual synapses during long-term potentiation (LTP) or long-term depression (LTD), collectively referred to as Hebbian plasticity, or globally during homeostatic scaling [8,9]. It is widely believed that changes in synaptic strength through Hebbian plasticity form the cellular basis of learning and memory, while homeostatic scaling is an important mechanism for bidirectional regulation of neuronal excitability and for maintaining synaptic strength within a dynamic range. In order to benefit cognitive processes such as learning and memory, at least one major target of sleep's restorative processes must be neuronal synapses [5]. The sleep homeostasis hypothesis (SHY) suggests that encoding information from experiences during wake requires a net increase in synapse strength and size through LTP-type mechanisms. Wake-related synaptic potentiation is then balanced during sleep by a widespread but selective weakening of synapses through homeostatic scaling-down to restore homeostasis and permit further learning and memory (Figure 1) [1,10,11]. Synapse strengthening during wake can lead to saturation, precluding further learning. Synapse weakening during sleep de-saturates synapses, allowing for new potentiation on the following day, renewing our daily capacity for learning. Furthermore, SHY predicts that sleep can promote memory consolidation by reducing the strength of weak synapses below a functional threshold, leaving potentiated "important memory" synapses functional, thereby enhancing synaptic signal-to-noise (Figure 1) [1].

Homeostatic scaling-down is engaged in cultured neurons *in vitro*, in response to sustained increases in neuronal activity. In cultured neurons this plasticity type is global, causing a multiplicative change in synaptic strength. Current evidence suggests that every synapse is weakened by the same factor, preserving the relative difference between synapses [9]. However, where weakening of synapses in cultured neurons during scaling is multiplicative and global, weakening synapses during sleep shows a selective down-scaling, a broad weakening of synapses but with some synapses spared or even potentiated [10-13]. Recent data show that sleep-specific patterns of electrical activity such as slow-wave activity in the cortex [14,15] and sharp wave ripples in the hippocampus [16] can drive this selective down-scaling. Thus, sleep may promote a broad weakening of synapses while at the same time, specific patterns of activity can shape this process by capturing specific synapses, allowing them to escape from scaling-down or even undergo LTP [17]. This protection of memory traces or engrams, may involve the synaptic replay events shown to occur in hippocampus during sleep [18]. Synapse weakening during scaling-down in culture or during sleep involves a reduction in post-synaptic AMPA-type glutamate receptors (AMPARs) [9,10,19]. Homer1a and mGluR1/5 are molecules required for scaling-down *in vitro* and also underlie the weakening of synapses during sleep in mice [10,20].

mGluR5 AND SLEEP

Type 1 metabotropic glutamate receptors (mGluR1/5) are post-synaptic GPCRs, heavily implicated in multiple forms of synaptic plasticity, learning and memory, and in several psychiatric and neurological disorders [21]. These receptors have a broad and overlapping expression pattern in the brain, with mGluR5 more heavily expressed in cortex, hippocampus and striatum, and mGluR1 more strongly expressed in cerebellum [21]. Several recent

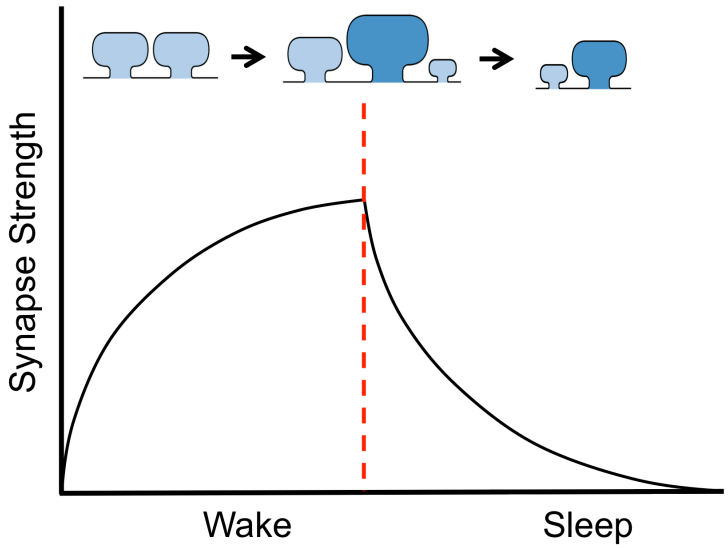

Figure 1. The sleep homeostasis hypothesis (SHY). SHY predicts that synapses undergo a net increase in strength during wake, through LTP-type mechanisms. Synapse strength is restored to baseline during sleep by selective homeostatic scaling-down.

studies strongly implicate mGluR5 in the homeostatic build-up of sleep need and in synapse remodeling during sleep.

In healthy human volunteers, prolonged wake of 33 hours resulted in an increase in the availability of mGluR5 in the cortex (receptors primarily on the cell surface) measured using positron emission tomography (PET) [22,23]. Increased slow-wave activity (SWA) or delta-band frequency (0.5-4Hz) during non-rapid-eye-movement (NREM) sleep is one of the most reliable markers of sleep-need [2]. SWA reliably increases following periods of wake and dissipates during sleep and is reliably upregulated following extended wake. In humans, SWA under basal or sleep deprived (SD) conditions correlated with mGluR5 availability and SD-induced increase in SWA correlated with the increase in mGluR5 availability compared to baseline [22]. PET imaging also showed increased mGluR5 availability during the sleep phase in rats [24]. mGluR5 mRNA or protein expression are not affected by sleep or SD [5,10,22], showing that the SD-induced increase in mGluR5 availability likely reflects increased targeting to the cell-surface independent of altered expression. Moreover, the build-up of sleep need seen by the SD-induced increase in SWA is strongly impaired in mGluR5 knockout mice compared to wild-type littermates [22,25]. Knockout mice also showed reduced time in rapid-eye-movement (REM) sleep and reduced NREM-REM transitions [25]. These findings suggest that mGluR5 forms part of the molecular basis for the homeostatic build-up of sleep need and transition to REM sleep. The increased availability of mGluR5 after SD could be interpreted as part of a mechanism that maintains vigilance following SD. However, the reduced SWA following SD in mGluR5 knockout mice rather suggests that mGluR5 is part of the "sensor" of sleep need and that mGluR5 is also part of the molecular basis for the restorative function of sleep.

mGluR5 has a rich pharmacology including selective agonists, antagonists, and allosteric modulators. Increased mGluR5 activity caused by treatment with positive allosteric modulators (PAMs) is strongly arousing in rodents and suppress sleep [26-28]. Conversely, treatment with negative allosteric modulators (NAMs) caused an apparent enhancement of NREM sleep, increasing NREM bout length and sleep time, partially at the cost of REM sleep [26]. These findings suggested that mGluR5 signaling sustains wake and that inhibition may enhance sleep. However, this view is challenged by a recent study that tested the effect of mGluR inhibition on memory consolidation [10]. Mice were trained in contextual fear conditioning (CFC), followed by injection with combined mGluR1/mGluR5 inhibitors. Drug treatment during the sleep phase caused enhanced fear memory in the trained and novel contexts indicating generalization of the contextual memory and poor memory consolidation, whereas drug treatment during the wake phase had no effect. This result shows that mGluR1/5 are actively engaged in the brain during sleep to promote memory consolidation. Therefore, while block of mGluR5 during sleep seems to increase sleep efficiency [26], this may actually impair the "output" of sleep, the restorative synaptic plasticity relevant for memory consolidation [10,20]. We propose

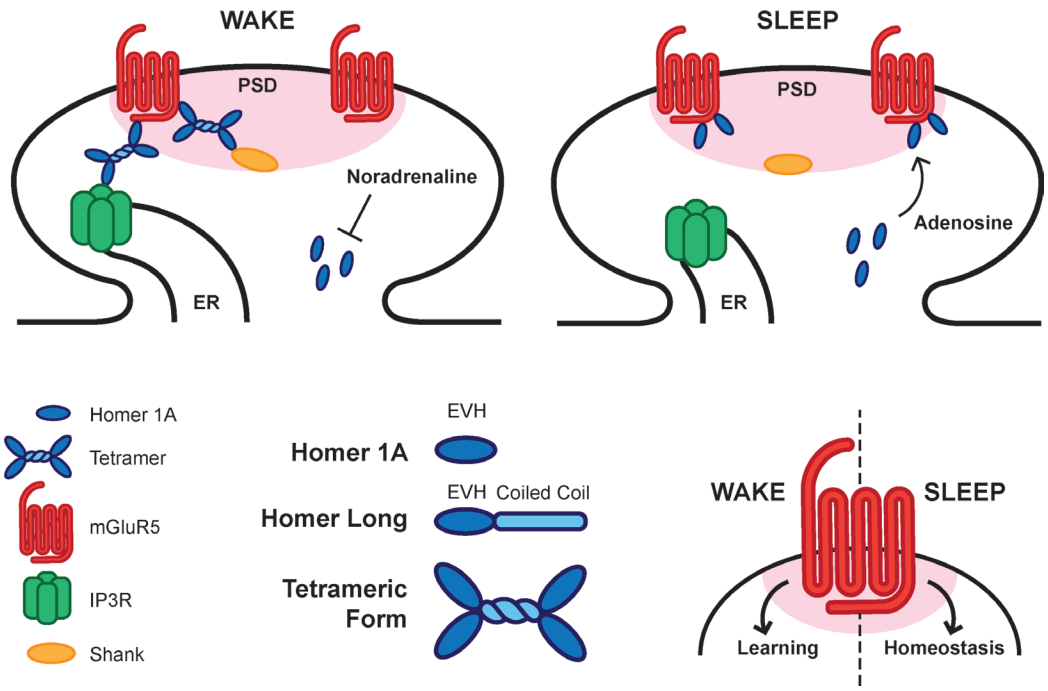

Figure 2. mGluR1/5 switch between wake and sleep-type signaling gated by Homer1a. Homer scaffold proteins include long forms that contain an EVH domain and coiled-coil domain that allows for the formation of a multivalent tetramer, and an activity-dependent short form, Homer1a, that contains only the EVH domain. During wake, long-form Homer couples mGluR1/5 to Shank scaffold proteins within the PSD and to IP3Rs in the endoplasmic reticulum. Homer1a targeting to the PSD is suppressed during wake by arousal-promoting noradrenaline. At the onset of sleep, drops in noradrenaline and increased levels of adenosine promote Homer1a targeting to synapses, where Homer1a acts as a dominant-negative to uncouple mGluR1/5-IP3R complex. Homer1a also promote agonist independent constitutive signaling of mGluR1/5. We propose a model in which mGluR1/5 switch between awake-type and sleep-type signaling gated by Homer1a.

a model where mGluR1/5 are actively engaged in synaptic plasticity and homeostatic processes during wake and during sleep, but where the output of this signaling pathway may be switched between "awake-type" and "sleep-type" modes of signaling (Figure 2). This model is described further below.

HOMER1a AND SLEEP

Homer proteins are synaptic scaffold proteins produced by three homologous genes Homer1-3. These genes produce constitutively expressed long isoforms containing an EVH domain that mediates protein-protein interactions, and a coiled-coil domain that allows long Homer to form multivalent tetramers (Figure 2) [29,30]. Long-form Homer proteins tether mGluR1/5 to their signaling partner, the IP3R, and anchor mGluR1/5 to the excitatory post synaptic density (PSD) by simultaneous direct binding of mGluR1/5 cytoplasmic tails and the core PSD scaffolds Shank1-3 or IP3R (Figure 2) [29,31-33]. The Homer1 gene can also produce a short splice variant called Homer1a, an activity-dependent immediate early gene, strongly induced in neurons by neuronal activity, learning, and following LTP [34,35]. Homer1a contains the EVH domain but lacks the coiled-coil domain, producing a natural dominant-negative effect by binding to mGluR1/5 but uncoupling these receptors from Shank and IP3Rs (Figure 2) [29].

In addition to the increase in SWA described above, humans and rodents typically exhibit sleep rebound behavior in response to SD: a reduced latency to enter sleep and increased sleep time and bout duration during recovery sleep [2]. A previous study using several strains of inbred mice showed clearly that the homeostatic increase in SWA following SD is under strong genetic control [36]. Subsequent studies suggested that polymorphisms and expression levels of Homer1a explain variations in this sleep rebound behavior [37,38]. These studies showed that Homer1a mRNA was strongly induced following SD, and upregulation of Homer1a transcript correlated with sleep rebound behavior in mice [37,38]. Deletion of Homer1a in mice reduced the ability of mice to sustain long periods of wake, suggesting that Homer1a is required for the restorative output of sleep [39]. However,

Homer1a knock-outs showed apparently normal increase in SWA in response to SD. Either Homer1a is more strictly related to the output of sleep and not the homeostatic drive for sleep, or the loss of Homer1a can be compensated for by other mechanisms that promote sleep drive, possibly involving regulation of the long-form Homer proteins by phosphorylation, or the interaction between Homer scaffolds and mGluR5 [40,41].

While Homer1a mRNA is expressed at higher levels during wake [37], the protein shows reduced targeting to synapses during normal wake, and enhanced synapse targeting during sleep or during SD [10]. Homer1a synapse targeting is suppressed by the neuromodulator noradrenaline, maintaining low-levels of Homer1a at synapses during periods of arousal. Conversely, Homer1a synapse targeting is promoted by increased adenosine signaling through adenosine A1 receptors (Figure 2) [10]. Noradrenaline is strongly associated with attention and arousal, while adenosine is one of the best characterized somnogens (sleep promoting substance). Extracellular levels of adenosine increase during prolonged wakefulness and promote sleep [2,42,43]. Because Homer1a expression is driven by neuronal activity and learning during waking, Homer1a is also able to link the wake-related history of individual neurons with the restorative functions of sleep. Therefore, by responding to levels of noradrenaline and adenosine, immediate early gene Homer1a can function as an integrator of previous waking plasticity, arousal and sleep need, and modulate the restorative output of sleep by altering the interaction of mGluR1/5 with the PSD and IP3Rs (Figure 2). Compelling pre-clinical data suggest that adenosine A1 receptor signaling also promotes Homer1a gene expression and mediates the short-term antidepressant effects of SD [44].

Recently, it was found that purified PSD components including Homer (long) and Shank, could spontaneously form phase separated liquid droplets *in vitro* [45]. Addition of purified Homer1a to this preparation caused a rapid dispersion of the PSD-like droplets [45], showing that Homer1a protein has strong dominant negative properties, relevant not only for mGluR1/5 signaling but also synapse structure. This observation offers mechanistic insights to the shrinkage and weakening of excitatory synapses observed during sleep [1,10,11].

mGluR5/HOMER1α SIGNALING DURING SLEEP

mGluR1/5 are coupled to Gq-type G-proteins, signaling through phospholipase Cβ, IP3R-dependent Ca^{++} release, and PKC. mGluR1/5 also signal through MAP kinase, mTOR and protein synthesis, endocannabinoid synthesis, and tyrosine kinases and phosphatases [21,46]. During wake, mGluR1/5 are anchored to the PSD and the IP3R through constitutively expressed long-form Homer1-3. During sleep, increased synaptic targeting of Homer1a, uncouples mGluR1/5 from IP3R throughout the cortex (Figure 2) [10], suggesting that mGluR-IP3R signaling is down-regulated during sleep. However, Homer1a binding has been shown to activate agonist-independent mGluR1/5 signaling [47], and this Homer1a-dependent, glutamate-independent signaling mode of mGluR1/5 was shown to drive weakening of excitatory synapses during scaling-down [20].

mGluR1/5 are involved in synaptic plasticity, and learning and memory [21], and activation of mGluR5 with PAM treatment is strongly arousing while inhibition with NAMs promotes consolidated sleep [26-28], strongly suggesting a role of mGluR1/5 signaling during wake. On the other hand, Homer1a-dependent constitutive mGluR1/5 signaling is involved in homeostatic weakening of synapses and memory consolidation during sleep [10,20]. Since mGluR1/5 become uncoupled from their effector the IP3R during sleep (Figure 2), this then raises the question of what are the relevant mGluR1/5 downstream signaling pathways that mediate synapse remodeling during sleep? Downstream targets of mGluR1/5 (MAP kinase, mTOR/protein synthesis, and the endocannabinoid system) are implicated in sleep and sleep-dependent memory consolidation [48-50]. Signaling of MAP kinase Erk1/2 is upregulated during sleep [10,51], and inhibition of mGluR1/5 during sleep, but not during wake, reduces the phosphorylation of Erk1/2, suggesting that MAP kinase signaling is at least one sleep-relevant mGluR1/5 downstream pathway [10]. Whether the mTOR and endocannabinoid systems active during sleep are downstream of mGluR1/5-Homer1a remains to be determined. Identification of mGluR1/5-dependent pathways engaged during sleep will be an important step in understanding the molecular basis for the restorative output of sleep and may facilitate the development of therapies specifically designed to enhance this restorative process in diseases associated with sleep disruption and cognitive impairments including ASD and AD [6,7].

SLEEP AND mGluR5 IN DISEASE

Sleep disruption is commonly associated with psychiatric and neurologic disease and is seen in a majority of patients with AD and ASD. Declines in sleep amount and quality are typical in aging humans, although whether this is due to dysfunction of sleep-promoting brain circuits or the homeostatic drive for sleep is debated [52]. AD is a pathological neurodegenerative disease defined by synapse degeneration, cell loss and progressive decline of cognitive functioning. Sleep disruption, in advance of any symptoms of cognitive decline, may predispose people to develop AD. Additionally, once an AD

diagnosis has been made, sleep disruption may be a primary driver of progressive memory impairments [52,53]. Synaptic loss in AD is linked to the accumulation of misfolded tau proteins, dysregulation of amyloid precursor protein (APP) processing and increases in Amyloid-beta (Aβ) deposition leading to the development of amyloid plaques. Extracellular levels of Aβ species are tightly linked to the sleep-wake cycle, with increasing levels during wake and decreasing levels during rest in both rodents and humans [53-56]. Chronic sleep deprivation in transgenic animal models leads to an increase in Aβ deposition while sleep promotion reduces Aβ levels [54].

mGluR5 and the cellular prion protein (PrP^C) form a protein complex that is known to contribute to AD pathogenesis by acting as a specific receptor for Aβ, amongst other putative receptors [57]. Aβ binding to the PrP^C-mGluR5 complex activates mGluR-dependent intracellular Fyn kinase signaling, leading to synapse dysfunction and elimination [58-60]. Although treatment with mGluR5 NAMs and mGluR5 knockouts show improved memory in an AD mouse model [61], inhibition/loss of the pathological Aβ/PrP^C signaling pathway may come at the cost of physiological mGluR5 signaling that is important for certain forms of synaptic plasticity [20]. Specific targeting of the Aβ/PrP^C signaling cascade via silent allosteric modulators (SAM) effectively prevents Aβ signaling by inhibiting the interaction between mGluR5 and PrP^C and rescues memory deficits independent of glutamate signaling [62]. SAM proves to be an efficient way of specifically targeting Aβ/mGluR5 signaling to limit AD pathogenesis. One possibility is that mGluR5 signaling activated by PrP^C and Aβ may be of the "wake-type" (Figure 2). Excess of extracellular Aβ may trap mGluR5 in this mode at the cost of the "sleep-mode" and thereby contribute to sleep disruption, similar to the findings that mGluR5 PAM treatment is strongly arousing and suppresses sleep [26-28]. While inhibiting aspects of pathological mGluR5 signaling may be effective in AD, treatments which specifically enhance restorative mGluR5 signaling during sleep may also be important to offset sleep disruption in AD patients.

Sleep disruption is seen in > 80 percent of patients with ASD [6]. Synapses have been identified as a major locus of disease in ASD and other psychiatric disorders [63,64]. The role of sleep in brain development is not fully understood, however, sleep seems to be important for synapse formation, stabilization, and pruning during early life. Moreover, early life sleep disruption in *Drosophila* causes a permanent alteration in social behavior [1,12,65,66]. Dysfunction in mGluR5 signaling, as well as mutations in associated Homer and Shank scaffolds are implicated in several ASD conditions [63,67]. We propose that an altered balance between the wake and sleep modes of mGluR signaling may contribute to sleep disruption and synapse dysfunction in ASD. Treatments designed to enhance the restorative mGluR signaling associated with sleep may be effective in reducing sleep disruption, and cognitive and behavioral phenotypes in ASD patients.

CONCLUSIONS

The molecular basis for the homeostatic drive for sleep and the resolution of sleep need is poorly understood. Synapses are believed to be one major locus of sleep need and the restorative functions of sleep that support cognition [1,5]. Recent literature support a role for mGluR1/5 and Homer1a in both the build-up of sleep need and the restorative function of synaptic down-scaling [10,22]. Alterations in mGluR1/5 signaling are implicated in many diseases, many of which also include sleep disruption. mGluR1/5 have been proposed as important therapeutic targets and have been tested in clinical trials. Our model suggests that mGluR1/5 undergo a switch in their signaling modes between wake and sleep, gated by the immediate early gene Homer1a (Figure 2). With this in mind, it is possible that therapeutic agents targeting mGluR1/5, NAMs for example, may normalize some aspects of mGluR1/5 signaling during wake, at the expense of the restorative aspects of mGluR1/5 signaling engaged during sleep [26-28]. Future investigations and trials into the effectiveness of mGluR1/5 therapeutics will need to account for the clear time-of-day effects of these drugs [10]. A better understanding of the precise mGluR1/5 downstream signaling pathways relevant for wake and sleep may allow for the development of more precise therapeutics that independently normalize these separate wake/sleep functions.

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