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Thalamocortical dynamics of sleep: roles of purinergic neuromodulation

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Abstract

Thalamocortical dynamics, the millisecond to second changes in activity of thalamocortical circuits, are central to perception, action and cognition. Generated by local circuitry and sculpted by neuromodulatory systems, these dynamics reflect the expression of vigilance states. In sleep, thalamocortical dynamics are thought to mediate “offline” functions including memory consolidation and synaptic scaling. Here, I discuss thalamocortical sleep dynamics and their modulation by the ascending arousal system and locally-released neurochemicals. I focus on modulation of these dynamics by electrically-silent astrocytes, highlighting the role of purinergic signaling in this glial form of communication. Astrocytes modulate cortical slow oscillations, sleep behavior, and sleep-dependent cognitive function. The discovery that astrocytes can modulate sleep dynamics and sleep-related behaviors suggests a new way of thinking about the brain, in which integrated circuits of neurons and glia control information processing and behavioral output.

Keywords

sleep; thalamocortical circuitry; oscillations; memory; astrocytes; ATP; adenosine

Introduction

Sleep is a behavior that is ancient and pervasive throughout the animal kingdom, yet the cellular and circuit mechanisms underlying sleep regulation are poorly understood. Importantly, the functional need for animals to spend much of their lives in an “offline” state is not clear. The quest for understanding the function(s) and regulation of sleep is one of the most interesting endeavors of modern neuroscience, not only due to the insights it provides for understanding normal brain function but also due to its translational impact given sleep disruptions in most neuropsychiatric disorders, including schizophrenia, bipolar disorder and epilepsy [1]

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Phenomenologically, sleep is characterized by a number of criteria that include species-specific postural changes, increased threshold to environmental stimuli and changes in global brain activity [2,3]. Such criteria have been observed in species ranging from fruit flies to mammals [4], and have been important in establishing sleep as a universal behavior among animals [5] (but see [6]). An additional and perhaps a defining criterion of sleep, as opposed to other expressions of behavioral inactivity, is its “homeostatic regulation”. While sleep is regulated by circadian mechanisms that ensure its appropriate expression in relation to environmental conditions such as the light/dark cycle and food availability [7], sleep drive increases as a function of prior wakefulness independent of circadian control [8]. For example, if sleep expression is hindered at a time when an animal normally sleeps, sleep is compensated in the animal’s active behavioral phase [9]. In humans, deprivation of sleep during the night normally results in enhanced sleep during the following day.

In mammals, global changes in brain activity have classically been described using electroencephalography (EEG); integrated extracellular field potentials reflecting subthreshold membrane potential changes in cortical neurons [10]. Along with the electromyogram (EMG)-- the electrical measurement of muscle activity-- the EEG is considered the gold standard for measurements of vigilance states [11]. The EEG shows changes in frequency and amplitude across the three vigilance states; wakefulness, non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). In NREM sleep, the EEG is dominated by slow waves in the 0.5–4Hz range whose amplitude and incidence correlates positively with sleep intensity [12]. Interestingly, slow waves appear to be homeostatically regulated similar to sleep behavior [9]. Brain dynamics during sleep, which include slow waves, are thought to mediate many of the hypothesized function of sleep including synaptic downscaling [13] and memory consolidation [14] (discussed in the following section).

Though much of sleep research in the last century has focused on neuronal mechanisms of sleep regulation, the role of electrically-silent glia in modulation of this behavior has recently been elucidated [15]. Astrocytes, the major subtype of glia in the mammalian neocortex, have classically been thought to play supportive roles. Research over the last two decades has shown that these cells have important neuromodulatory actions [16–18] that can impact circuit function [19] and behavior [15]. In the remainder of this review, I will discuss sleep dynamics in thalamocortical circuits, highlighting the role of neuromodulation in shaping these dynamics. I will subsequently discuss neuromodulatory functions of astrocytes focusing on the role of purinergic gliotransmission in controlling neuronal circuit function, sleep dynamics and sleep behavior.

Proposed functions of sleep

Though sleep may have many functional roles, two “sleep function” hypotheses involving internal computations have recently been introduced and may explain why sensory disengagement is a feature of sleep. One hypothesis is based on the original discovery by Wilson and McNaughton [20], where using multielectrode recordings they found evidence for hippocampal cell “reactivation” during sleep. That is, hippocampal cells that encoded overlapping spatial locations during awake experience, where more likely to fire together during sleep. More recently, sequential “replay” of place cells resembling that seen during awake behavior has been shown [21]. Replay occurs during 200–300Hz field potential hippocampal dynamics called sharp wave ripples (SWR) [22]. Disrupting SWR with electrical stimulation disrupts memory consolidation, providing evidence that hippocampal replay may be essential for memory consolidation [23,24]. The second hypothesis, proposed by Tononi and Cirelli, is based on the observation that during wakefulness many genes involved in synaptic potentiation are expressed [25]. Corroborated by biochemical and

electrophysiological evidence that wakefulness is associated with net potentiation of excitatory synaptic transmission [26,27] which would increase space and energy demands, they posit that sleep is a state in which synapses are scaled down while preserving their relative strength [13]. Certain thalamocortical sleep dynamics are thought to contribute to synaptic scaling as their low-frequency is conducive to LTD-like synaptic de-potentiation [28]. These two hypotheses are not mutually exclusive, as replay and potentiation of salient memories may occur concurrently with overall net synaptic de-potentiation and scaling and improved mechanistic understanding of these processes will shed light on the requirement of sleep states in brain function.

Thalamocortical dynamics in sleep

The six layered neocortex is a defining feature of the mammalian brain, and is a derivative of the vertebrate dorsal pallium, an evolutionary conserved vertebrate structure [29]. Neocortical evolution has been matched by evolution and expansion of thalamic projections [29,30]. While thalamocortical projections are classically thought to relay information to the neocortex, recent evidence suggests that thalamocortical neuronal firing impacts neocortical states [31,32]. Depending on their initial resting membrane potential, thalamocortical (TC) neurons are able to either reliably transmit spike trains or initiate oscillatory burst firing in response to the incoming synaptic drive [33]. This ability is conferred by the repertoire of voltage-gated ion channels that TC neurons express. In particular, T-type Ca^{2+} channels, which are inactivated at resting membrane potentials of > -65 mV allow for oscillatory burst firing when TC neurons are hyperpolarized below -65 mV [34]. These biophysical properties are shared by neurons of the thalamic reticular nucleus (TRN), which provide the major source of synaptic inhibition to thalamic nuclei [35]. The de-inactivation of T-type Ca^{2+} channels initiates a low-threshold Ca^{2+} spike when TC or TRN neurons are synaptically driven. In earlier stages of sleep, with moderate levels of hyperpolarization, synaptic input to TRN and TC neurons results in burst firing and the generation of spindle oscillations (7–14Hz) [36], which are transmitted to the cortex. Interestingly, the incidence of spindles has been shown to positively correlate with the threshold of sensory stimulation required for sleep disruption [37], pointing to a role for spindle-generating circuitry in sensory gating. This is consistent with findings that spindle density is greatly reduced in patients with schizophrenia, a disorder of sensory gating [38]. In addition, spindle oscillations are enhanced after learning [39,40], and many spindles synchronize with hippocampal SWRs (discussed earlier) [41,42], pointing to a role for spindles and the underlying thalamic circuitry in sleep-dependent memory consolidation. Understanding precisely how that happens (potentiation of cortical synapses vs. filtering of incoming sensory signals to allow for internal hippocampo-cortical communication), and how it is modulated by subcortical and local factors (see later sections) will be of major importance.

As TC/TRN neurons become more hyperpolarized, their inter-burst interval widens resulting in the appearance of delta oscillations (1–4Hz) [36], also transmitted to cortex [43]. Evidence that the thalamus is the generator of cortical delta oscillations comes from both slice and *in vivo* intracellular recordings, showing clock-like delta oscillations in individual thalamocortical neurons [44,45]. More recently, knockout of potassium channels preferentially expressed by thalamic neurons resulted in marked attenuation of low frequency cortical oscillations during sleep [46,47]. Importantly, sleep itself was less stable in these mice suggesting that sleep dynamics may drive sleep behavior.

Though spindles and delta oscillations are prominent sleep rhythms, the cortical slow oscillation is the most defining rhythm observed during sleep. The slow oscillation is a <1 Hz rhythm that is observed at multiple levels of organization in the brain during sleep [48]. For example, slow oscillations have been described as traveling waves in the human brain [49].

On a cellular level, neurons in a number of different cortical areas fluctuate between depolarized (UP) and hyperpolarized (DOWN) states [50]. The UP state is characterized by barrages of synaptic activity, a plateau depolarization, and action potential firing, while the DOWN state is characterized by cell hyperpolarization and silence [51]. These membrane potential fluctuations are tightly synchronized to the local field potential, in which waves of field potential slow oscillations trigger precise sequential firing of pyramidal neurons [52]. Understanding the detailed circuit mechanism for generating slow oscillations will be important for dissecting other sleep rhythms as slow oscillations organize delta and spindle oscillations [48]. Furthermore, an interest in the role of slow oscillations in mediating sleep function(s) has recently been bolstered by the finding that boosting these rhythms during sleep enhances human memory [53].

Ascending neuromodulators impact thalamocortical dynamics

Though thalamocortical dynamics are generated by synaptic interaction among TRN, TC and neocortical neurons, they are modulated by ascending inputs originating from nuclei in the brainstem, hypothalamus and basal forebrain [54]. Among these is the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT); brainstem areas containing cholinergic neurons that fire preferentially during wakefulness and REM compared to NREM. Acetylcholine (ACh) released by these neurons can have complex effects on thalamic, hypothalamic and basal forebrain neurons [7]. Monoaminergic neurons in the upper brainstem and caudal hypothalamus, including the noradrenergic locus coeruleus (LC), serotonergic dorsal raphe (DR), dopaminergic ventral periaqueductal grey matter and histaminergic tuberomammillary neurons, lateral hypothalamic peptidergic neurons (orexin/hypocretin-containing), and basal forebrain neurons (ACh or GABA-containing) [55] project directly to the cortex [56]. Activation of these nuclei promotes behavioral and electrographic arousal [57], and thus these are thought of canonical “arousal centers” [56]. These nuclei receive inhibitory input from the ventrolateral preoptic area (VLPO), a group of GABAergic neurons that fire preferentially during sleep [58]. One synthesis of subcortical sleep/wake neuronal circuitry is proposed by Saper in his flip-flop switch model of sleep regulation [7]. In this model, brainstem and hypothalamic sleep related circuitry is viewed as mutually inhibitory elements in which activity in one of the competing sides shuts down inhibitory inputs from the other side, and therefore disinhibits its own action. This ensures that when arousal centers are “on”, they turn off sleep centers and vice versa, ensuring sharp state-transitions. Though elegant, this model may not be fully compatible with observations of sub-states of arousal, such as tonic alertness, selective attention and sensory-disengagement which exhibit different electrographic signatures and may differentially recruit the canonical sleep wake circuitry.

Local Sleep

Based on studies of unihemispheric sleep in marine mammals, it is widely appreciated that the minimal unit for sleep expression may not encompass the entire brain [59]. However, defining which parts of the brain engage in sleep expression is a challenge. The discovery of regional differences in slow wave expression across the cortex has generated significant excitement, as it supports the notion that sleep may be a use-dependent process, driven by local circuitry [49]. This is further supported by discoveries that local slow wave expression correlates with previous sensory, motor or cognitive demands of the cortex in prior wakefulness [60]. Recently, Krueger and colleagues have suggested that the minimal unit of sleep is the cortical column, and that sleep behavior results from coalescence of many cortical columns engaging in “sleep-like states” [61]. Though our knowledge of regional cortical states is in its infancy, Petersen and colleagues have shown that cortical neurons in the mouse somatosensory cortex can express UP and DOWN states when the mouse is in

quiet wakefulness [62], This membrane bistability disappears when the mouse engages in whisking behavior [63]. Work from McCormick's group has shown that delta oscillations can exist in the visual cortex of ostensibly awake mice [101]. Thus, sleep-like dynamics may be expressed during wakefulness and understanding both their local regulation and link to global sleep behavior would be of great significance, helping to elucidate how and why the brain generates sleep.

Local neuromodulation of thalamocortical dynamics by adenosine

In addition to circuit modulation via afferent projections, neuromodulatory substances can be released locally within neuronal circuitry via non-synaptic mechanisms. Such substances include peptides such as tumor necrosis factor alpha (TNF- α), insulin and growth hormone (GH) which locally regulate the expression of slow wave activity in the cortex [64], and small molecules such as nitric oxide and adenosine, powerful modulators of sleep homeostasis [65].

On a behavioral level, adenosine satisfies the criteria for an endogenous sleep factor. Its levels correlate positively with the amount of time spent in wakefulness [65–67], infusing it (or its agonists) into the brain promotes sleep [68,69], and antagonizing its effects promotes wakefulness [70–72]. Increasing adenosine availability through the infusion of adenosine kinase inhibitors, adenosine deaminase inhibitors, and an adenosine transport blockers also promotes sleep [65,73]. Interestingly, caffeine, one of the most widely used substances in the world, is thought to exert its wake-promoting effects by adenosinergic mechanisms [74,75]. Additionally adenosine deaminase polymorphism profoundly impacts sleep intensity and duration in humans [76]. Thus, deconstructing the cellular and circuit mechanism of adenosinergic regulation of sleep is likely to result in significant translational benefits.

On a cellular level, adenosine has been shown to act through several receptor subtypes, namely, A₁R, A₂AR, A₂BR and A₃R. In sleep studies, A₁Rs and A₂ARs have received particular attention due to their expression patterns in the brain, the availability of selective agonists and antagonists and selective molecular manipulation of genes encoding their receptor subtypes[2]. A₁R are expressed at high levels throughout the brain, particularly in the cortex, hippocampus, thalamus and cerebellum [77]. A₂ARs are expressed most strongly in the striatum [78]. A₁R are Gi-coupled, exerting inhibitory effects on neuronal excitability and synaptic transmission, while A₂ARs are Gs-coupled, exerting opposite electrophysiological effects. Activation of these two receptors is thought to promote sleep through a number of proposed mechanisms. For example, activation of A₁R promotes sleep at the level of ascending arousal system—inhibition of PPT/LDT neuronal activity [79], inhibition of cholinergic basal forebrain neuron [79]. Importantly, A₁R activation can have direct sleep-rhythmogenesis enhancing effects on the thalamocortical system. Circuit analysis of thalamocortical neurons in acute brain slices has shown that adenosine enhances burst firing in these neurons in the absence of other modulatory input [80]. A₂AR on the other hand may promote sleep by activating sleep-active VLPO neurons [81].

Infusion of adenosine A₁R agonists into the brain not only results in enhancement of sleep, but also in enhancement of slow wave activity (SWA; 0.5–4Hz frequency band oscillations) during sleep [69,82]. SWA activity is a marker of homeostatic sleep pressure, as its power positively correlates with the amount of prior wakefulness [8]. A₁R antisense infusion into the basal forebrain of rats resulted in attenuation of the behavioral and electrographic homeostatic sleep response [83].

A₁R knockout studies aimed at understanding the role of A₁R in sleep regulation were initially controversial. A study by Sternberg et al [84], showed that A₁R knockout animals

had no sleep phenotype. However, it is important to note that one needs to interpret studies from constitutive knockouts with caution. The constitutive absence of A₁R throughout development is likely to result in compensatory changes that may mask important physiological functions that this receptor signaling pathway has. This is especially true given the role of A₁R in brain development [85]. In fact, a recent study by Bjorness and Greene has shown an important role for A₁R in sleep homeostasis using a conditional, forebrain-specific, A₁R knockout animal [86]. In this study, the authors used a novel method for controlled sleep restriction, where sleep time was limited to a total of 4 hours across the course of the total 24 hours. During restricted sleep, the expression of SWA was attenuated by forebrain specific knockout of the A₁R.

Astrocytes release ATP which contributes to extracellular adenosine

The discovery that astrocytes release chemical transmitters has revolutionized the study of the brain, as it added a layer of complexity to neuronal network function in which electrically silent glia can have neuromodulatory functions [16,18,87–89]. Gliotransmission, the process of transmitter release by astrocytes is mechanistically diverse and may occur through multiple molecular pathways including synaptic-like vesicles [90], large peptide-containing vesicles [91], lysosomes [92] anion channels [93], and connexin/pannexin hemichannels [94]. Additionally, astrocytes can release a number of transmitters including ATP, glutamate and D-serine [95]. [see contribution by Lalo et al in this issue]

The use of molecular genetics to understand the role of vesicular gliotransmission in neurophysiology resulted in the discovery that astrocytes release ATP through a SNARE-dependent mechanism [96]. Astrocytic ATP is rapidly (~200msec) degraded to adenosine which preferentially acts on A₁R [96,97]. These discoveries were made possible by the generation of transgenic animals in which the cytoplasmic domain of synaptobrevin II was specifically and conditionally expressed in astrocytes [96]. Given the role of synaptobrevin II in the formation of the SNARE-complex that is necessary for vesicular docking and fusion [98,99], the overexpression of its cytoplasmic domain is thought to inhibit vesicular release by a dominant negative mechanism (dnSNARE).

Electrophysiological experiments carried out on acute hippocampal slices derived from dnSNARE animals revealed that the molecular attenuation of vesicular gliotransmission resulted in enhancement of basal synaptic transmission, attenuation of paired-pulse facilitation and attenuation of theta-burst induced long term potentiation (LTP) [96]. These electrophysiological effects were mimicked in wild type slices by A₁R antagonists [96], and the dnSNARE electrophysiological phenotype was rescued by CCPA an A₁R agonist [96]. Phenotypic rescue was also possible with extracellular perfusion of ATP, an effect that disappeared when extracellular 5'-ectonucleotidase inhibitor (ARL67156) was additionally perfused or when the A₁R antagonist (CPT) was perfused. Finally, optical imaging of extracellular ATP revealed a reduction in slices derived from dnSNARE animals compared to wild type littermates. The combination of the aforementioned experiments demonstrated that astrocytes, through a SNARE-dependent mechanism, release ATP that is rapidly degraded to adenosine and that astrocytic adenosine has powerful modulatory effects on hippocampal synaptic transmission and plasticity.

More recently, astrocytes of the brainstem chemoreceptor area have been shown to respond to local increase in pH by an increase in their intracellular Ca²⁺ [100]. In response to this increase in Ca²⁺, astrocytes release ATP which causes activation of nearby chemoreceptor neurons. Driving astrocytes optogenetically, by activating the light-activated ion channel, channelrhodopsin 2 (ChR2) resulted in astrocytic release of ATP and an enhancement of the respiratory rhythm *in vivo* [100]. In contrast, driving astrocytes optogenetically in the

subthalamic nucleus resulted in neuronal suppression likely due to ectonucleotidase-mediated degradation of ATP to adenosine, which activated A₁R on these neurons. Thus, it may be plausible to hypothesize that the relative activity of ectonucleotidases in brain regions determines the sign of purinergic gliotransmission.

Astrocytic modulation of sleep and cognition

The discovery that astrocytes regulate extracellular adenosine in multiple forebrain regions led to the hypothesis that astrocytes may regulate sleep homeostasis. Reversible attenuation of gliotransmission in mice allowed for the discovery that astrocytes, indeed, regulate sleep homeostasis by adenosinergic mechanisms [15]. EEG recordings revealed an attenuated SWA phenotype under baseline conditions when gliotransmission was genetically inhibited. This reduction in spectral power of the EEG was state-specific, as SWA activity was only attenuated in NREM, but not wakefulness or REM in dnSNARE mice. This decrease in SWA was reversible when transgene expression was suppressed in dnSNARE mice as they exhibited a similar phenotype to their wildtype littermate when gliotransmission was restored. Importantly, this SWA activity phenotype manifested at the cellular and circuit level, where intracellular recordings of cortical neurons *in vivo* revealed a decrease in UP state probability of cortical neurons when gliotransmission was attenuated. Local field potential (LFP) recordings demonstrated the local network correlate of this phenomenon, demonstrating that gliotransmission can impact the genesis of sleep rhythms at the local circuit level by impacting synaptic transmission at multiple loci [19].

To test whether this electrographic phenotype had a behavioral consequence, the homeostatic sleep response was investigated while gliotransmission was manipulated. It was found that dnSNARE animals exhibited an attenuated behavioral and electrographic homeostatic sleep response to six hours of sleep deprivation at the beginning of their rest cycle compared to their wildtype littermates; both the enhancement in SWA and increased sleep time following sleep deprivation were attenuated. Interestingly, both these phenotypes were reversed upon transgene suppression in dnSNARE animals. Thus, reversible inhibition of gliotransmission reversibly attenuated the homeostatic sleep response, a fundamental aspect of sleep behavior. This phenotype was mimicked by intracerebroventricular infusion of A₁R antagonist (CPT) via microosmotic minipumps into wildtype animals. Additionally, dnSNARE animals showed an attenuated behavioral response to acute injections of CPT but not to the A_{2a}R-selective antagonist (ZM 241385), concluding that the dnSNARE phenotype can be explained by purinergic mechanisms. Furthermore, while accumulation of sleep pressure prevented memory consolidation in wild type animals, dnSNARE mice showed resistance to the effects of sleep deprivation on memory. A detailed investigation of this phenomenon is likely to provide insight into mechanisms of cognitive impairment secondary to sleep loss. Additionally, region-specific manipulation of astrocytic function using genetic, pharmacologic and optic approaches will provide mechanistic insight into how precisely astrocytes regulate SWA and sleep behavior, as many outstanding questions regarding whether the effects seen in dnSNARE animals can be attributed to local cortical modulation or more global modulation at the level of basal forebrain and/or brainstem.

Conclusions

Though sleep signals behavioral inactivity, the brain remains quite active during this state. In particular, the thalamocortical system generates a number of dynamics including, spindles, delta and slow oscillations which may be key to mediating hypothesized functions of sleep, such as synaptic scaling and memory consolidation. Much progress has been made on understanding the genesis and modulation of these dynamics. In addition to afferent input from the canonical ascending arousal system, the thalamocortical circuitry can be modulated

by locally released neurochemicals. One such chemical is adenosine, a substance whose extracellular levels are controlled by electrically-silent astrocytes. These cells release ATP through a vesicular pathway, which is degraded to adenosine and acts on neuronal A₁Rs to regulate synaptic transmission. Genetic inhibition of astrocytic vesicular transmitter release has revealed that astrocytes modulate sleep rhythmogenesis, sleep behavior, and sleep-related cognitive functioning by purinergic mechanisms. This highlights the integrated nature of brain circuits in which slow-signaling glia can modulate fast neuronal processes by releasing neuromodulators (Summary Figure). Investigating neuron-glia interaction in sleep will likely further our understanding of its function and regulation, and may provide therapeutic targets of sleep disruption in neuropsychiatric illnesses.

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Figure. Thalamocortical sleep dynamics emerge from astrocytic-neuronal networks

Top: Sagittal section of mouse brain highlighting cortex, thalamus and thalamic reticular nucleus (TRN) as an interactive system (arrows). Cellular-level oscillations are shown next to the relevant circuits which give rise to sleep dynamics. Bottom Left: three dimensional relationship between astrocytes and neurons; astrocytes enwrap neuronal cell bodies and processes. Bottom right: the tripartite synapse; astrocytes release a number of neuromodulatory substances, namely glutamate, D-serine and ATP. Glutamate and D-serine act on neuronal NMDA receptors while ATP is degraded to adenosine and act on adenosine A1-receptors, a modulator of sleep rhythms and sleep behaviors.