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The adenosine-mediated, neuronal-glial, homeostatic sleep response

Robert W. Greene[1,2,3], **Theresa E. Bjorness**[1,3], and **Ayako Suzzuki**[1]

[1]UT Southwestern Medical Center, Dallas TX

[2]International Institute of Integrative Sleep Medicine, Univ Tsukuba, Japan

[3]VAMC, Dallas TX

Abstract

Slow wave activity (SWA) during slow wave sleep (SWS) is the best indicator of the sleep homeostasis. The intensity of the SWA observed during SWS that follows prolonged waking is directly correlated with the duration of prior waking and its intensity decays during SWS suggesting a buildup and a resolution of sleep need. This sleep-homeostasis related SWA results from a buildup and decay of extracellular adenosine that acts at neuronal adenosine A1 receptors to facilitate SWA and is metabolized by adenosine kinase found in glia. This local neuronal-glial circuit for homeostatic SWA is primarily under the requisite control of two genes, the *Adora1* and *Adk*, encoding the responsible adenosine receptor and adenosine's highest affinity metabolizing enzyme.

1. Sleep Homeostatic Response Phenomenology

We have all experienced that, the longer we stay awake, the more likely we are to go to sleep and, the longer we stay asleep the more likely we are to awaken. This correlation is quite variable since it is difficult to control wake-promoting or arousing stimuli (of both external and internal origin) that interfere with the transition to sleep and the transition to wake. However, a very powerful correlation exists between previous wake duration and the intensity of sleep slow wave activity (SWA), expressed most prominently during the ensuing non-REM sleep or as it is also aptly called, slow wave sleep (SWS)(1, 2).

SWA is recorded from the EEG which is a field potential recording, conducted by the cerebral spinal fluid from the brain tissue to the surface of the brain and, in attenuated form, to the surface of the scalp. The intensity of SWA is quantified as the power of the EEG recording within the frequency range of 0.5–4.5 Hz (also called delta power), derived from a Fast Fourier Transform (FFT) of the EEG signal. The amplitude of the FFT power in the

Correspondence to: Robert W. Greene.

delta range, reflects both number of neurons (electrical generators) involved in the generation of the signal and the synchronicity of their activity.

The large amplitude of SWA power during sleep reflects the relatively high participation of cortical neurons in synchronous shifts in membrane potential from hyperpolarized potentials to more depolarized potentials and back again (3). It is this synchronous shift in membrane potential of single cortical neurons that generates the slow waves. During the hyperpolarized plateau (down-state) the neurons are quiescent and during the up-state they fire with only slightly less frequency than what is observed during waking (3, 4). Thus, during SWS, cortical neurons tend to shift their membrane potential synchronously between up and down membrane potential plateaus, to generate SWA and this SWA is tightly correlated with previous waking time. SWA is accordingly, considered a marker for sleep homeostasis, being increased with high sleep need (previous time spent predominantly awake) and decreased with low sleep need (previous time spent predominantly asleep) (5, 6).

SWA during waking increases on transition to SWS by more 1.5X, irrespective of the previous time awake or of circadian rhythm. This initial increase is largely due to a decrease in arousal system activity (6) and is not part of the homeostatic sleep response. Over and above the transitional increase of SWA in SWS, there is a homeostatic, SWA portion that correlates with previous time awake. During a SWS episode, SWA exponentially decreases with a specific time constant under baseline conditions that is characteristic of the genetic makeup of the animal. Interestingly, this rate of decay is slowed (time constant for decay increases) by sleep deprivation (6), suggesting that not only does SWA directly, correlate with sleep need buildup but its decay during SWS may also reflect the resolution of sleep need.

The effect of arousal on wake duration is powerful enough to overcome the propensity to fall asleep even when sleep need is high. For example, despite having stayed awake for a long duration, an arousing stimulus can shorten sleep time. An example may be a distressing phone call in the early morning that results in a long delay before transition back to sleep and perhaps fitful sleep thereafter. In experimental sleep deprivation studies, arousing stimuli are employed to sleep deprive a mouse or a rat to overcome high sleep need. Similarly, a genetic disruption of potassium channels as with the *Shaker* null flies, increases CNS excitability and decreases sleep time, while preserving a sleep homeostatic response (7, 8). In this case, the arousing stimuli result from a generalized increase of neuronal excitability in the absence of the *Shaker* gene. Pharmacologically, a benzodiazepine can decrease excitability and increase sleep time. Besides external and genetic activation of arousal systems, activation can be derived from a number of internal sources, including circadian (9), hunger (10) or other emotive influences. Increased arousal from any source, will cause increased wake time and increased sleep need. It follows that the increased sleep need will induce an increased homeostatic sleep response.

In this review, we have not addressed the interaction between the circadian and sleep homeostatic systems (recently reviewed in (2)), despite their overlapping downstream targets. One important example of overlap is the control of metabolism (11) (other aspects of

interaction are reviewed in (2)). There is ample possibility for indirect effects on sleep homeostasis via feedback from any of these target systems.

The circadian system may exert its most direct effects on sleep through the modulation of the arousal systems to alter wake duration. Wake duration, in turn, is directly correlated with the sleep homeostatic response (illustrated in figure 2). Nonetheless, the circadian system is likely to have other effects on sleep besides the modulation of arousal, but the mechanism(s) of action have not been clearly defined. In this review, we have focused on some major factors directly affecting the sleep homeostatic response but nonetheless, recognize that the circadian system clearly interacts with the homeostatic sleep system to control sleep as posited in the 2-process model of sleep regulation (2).

2. Mechanisms controlling the sleep homeostatic response

Arousal system neuronal activity drives waking and the duration of waking correlates with the sleep homeostatic response, so it follows that persistent arousal system neuronal activity also correlates with an increased sleep homeostatic response. One of the most important arousal related systems is the noradrenergic (NE) system of the Locus Coeruleus (LC). Optogenetic stimulation of this system results in high levels of arousal (12).

Selective, pharmacological depletion of NE from the LC with *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4), results in an attenuation of the sleep homeostatic response (13), namely an attenuation of SWA power, especially at the lower 0.5–1.5Hz range during NREM sleep. These findings are consistent with the necessity of an increased arousal tone mediated specifically by the LC for a normal homeostatic sleep response. A particularly important finding from this study was that sleep duration was relatively unaffected by chronic depletion of NE (13). Two important implications may be derived from the absence of an effect on sleep duration: first, NE is not necessary for the maintenance of normal amounts of wake, nor is it necessary for the normal sleep duration rebound observed in response to sleep loss. This dissociation of the SWA homeostatic sleep response from sleep duration has also been observed following the loss of the adenosine A1 receptor (ADORA1) as described below.

While LC activity is associated with increased thalamocortical neuronal activity, other monoaminergic or cholinergic arousal systems can mediate an increase in arousal tone, raising the question of whether other arousal mechanisms can induce a homeostatic sleep response. Remarkably, based on the selectivity reported for NE-depletion by DSP-4 (13), NE appears to be required for the typical SWA rebound homeostatic sleep response to prolonged waking (as noted above), but this does not rule out a homeostatic role(s) for other arousal related systems. NE also appears to be necessary for the circadian-driven enhancement of the SWA response that immediately follows the active (prolonged waking) phase.

A recent neurochemical study examining sleep-loss-induced HOMER1a association with synaptic PSD95 protein (14), showed that beta- and alpha-receptor antagonists could prevent the normal NE-mediated inhibition of HOMER1a-PSD95 binding. This provide a

correlation between waking induced NE tone and the interference with synaptic PSD95-Homer1a binding. During sleep, NE-tone decreases and the NE-mediated interference subsides, allowing Homer1a-PSD95 binding to proceed and presumably weaken the synapses. In summary, LC mediated NE tone may be required to drive the sleep homeostatic SWA response and its associated synaptic neurochemistry that is gated by the transition to NREM to directly reduce synaptic strength.

An important consequence of increased firing of most neurons in the mammalian CNS during wake, compared to other states, is a locally controlled, but globally distributed increase in extracellular adenosine (Ado). Ado can mediate a negative feedback inhibitory tone onto neurons through adenosine A1 receptors (ADORA1) in response to demands on the metabolic state of local neural tissue (15, 16). The inhibitory tone has been demonstrated on neurons of the cholinergic arousal system, suggesting a mechanism for activity induced reduction of arousal (17). It is worth noting that the Ado effect in the cholinergic arousal center is a local network effect yet, because of the divergent projections of the cholinergic neurons, their Ado mediated inhibition globally reduces the cholinergic-tone (17) and, by a similar Ado-ADORA1 mechanism, NE tone as well (18).

More generally in CNS tissue, an increase in the ratio of metabolic demand (i.e. neuronal activity)/metabolite availability (like, O_2 or glucose) is associated with an increase in extracellular Ado. At the synaptic level the increase in demand includes an increase in glutamate synaptic activity that is well within the normal physiological range. This activates NMDA receptors to increase Ado acting at ADORA1s (19). Notably, prolonged waking is sufficient to increase Ado in the basal forebrain and throughout thalamocortical structures where the increase can be measured by micro-dialysis (20, 21).

A sleep-relevant electrophysiological effect of Ado mediated by ADORA1 on thalamic and cortical neurons is to enhance SWA by increasing the G-protein inwardly rectifying current, decreasing hyperpolarization-activated inward current and increasing pre-synaptic inhibition (22). All three of these ADORA1 induced changes work together to facilitate burst firing in the thalamocortical neurons (23) that can facilitate SWA as well as the cortical neuronal tendency to fire with SWA oscillations.

The Ado tone results from local neuronal activity. However, local neuronal activity is globally driven by arousal center activation during waking. Thus, a global arousal tone may be associated with a globally distributed Ado tone. Furthermore, descending glutamatergic input to sub-cortical arousal centers can locally increase inhibitory Ado-ADORA1 tone in these same arousal centers (17, 19). This results in two systemic ADORA1 effects on thalamo-cortical targets; 1) a global decrease in arousal tone that will enhance SWS-SWA (21, 24) and a facilitation of the transition from waking to sleep (25) that is permissive to SWS-SWA expression; and 2) a local activation ADORA1 neuronal currents that pre-dispose to SWA firing patterns, at the cellular level. This ado-ADORA1-enhancement of SWA is necessary for the homeostatic sleep response of rebound SWA in response to sleep deprivation (22).

When the *Adora1* is conditionally knocked out from forebrain glutamatergic neurons (primarily pyramidal cells) in mice, the SWA rebound response is absent. SWA expression itself is not prevented, since there is an increase of more than 50% SWA power on transition from waking to SWS even in the absence of *ADORA1* in forebrain glutamatergic neurons. However, the further increase of SWA that is present in proportion to previous waking time over and above this transitional increase (i.e. rebound following prolonged waking) is missing (6, 24). Thus, ADORA1 is necessary for the expression of the sleep homeostatic response.

The further increase of homeostatic SWA amounts to an increase of more than 350% of baseline waking SWA (6). The SWA response to increased waking time can be seen across the circadian cycle. At the end of a wake phase, just before lights on (ZT=0) for a mouse, sleep need is high. At the end of the sleep phase, just before lights off, sleep need is low. The sleep need is tracked by the SWA observed during SWS (figure 1). The “further increase” of SWA is the homeostatic sleep response, thus implicating Adora1 as a homeostatic sleep response gene. The resolution of sleep need may be observed as a decay of SWA across the circadian sleep phase or, following sleep deprivation-evoked SWA-rebound, as a decay of the SWA-rebound in wildtype mice. The decay is missing (as is the rebound) in *Adora1* mutants (Figure 1) suggesting its dependence on ADORA1 activation by Ado. It thus seems likely to reflect the decrease in extracellular concentration of Ado during NREM sleep. This hypothesis was tested by deleting the gene encoding the highest affinity metabolic enzyme for Ado, adenosine kinase (Adk). Adk is found predominantly only in the glia in adult mice(26), implicating a neuronal-glial circuit in the control of Ado and hence in the control of the sleep homeostatic response. Adk binds ATP and Ado and releases ADP and AMP. The velocity of the enzyme with respect to Ado metabolism is determined by the ATP/ADP*AMP ratio. Thus, Adk is well positioned as a metabolic sensor to link glial metabolic state to extracellular Ado and during SWS, SWA. Indeed, when Adk is selectively deleted from glia (but not from neurons) the rate of SWA decline during SWS is remarkably slowed in association with increased SWA and extracellular Ado during both SWS and waking (6). Together these observations suggest that the metabolic state of the glia controls the homeostatic sleep response and its resolution. Thus, two genes, *Adora1* and *Adk* control the homeostatic sleep response by modulating the Ado system in the cortico-thalamic system of mammalian CNS (Figure 2). Sleep need is mediated by Ado acting at ADORA1s and it resolves through Ado’s metabolism by glial Adk.

Interestingly, knockout of either Ado gene has relatively little effect of sleep time. Since sleep duration is primarily a function of arousal system activity, it appears that arousal and sleep homeostasis can be dissociated by disrupting the Ado system that links the two (6, 24). On the other hand, different experimental methods of sleep deprivation of the same duration, lead to different levels of arousal with relatively small effect on homeostatic SWA (27). One may, nonetheless speculate that waking activity that especially activates the LC, would elicit a stronger sleep homeostatic response based on the findings that depletion of NE reduces this same response (13).

Normally, arousal prolongs waking and increases sleep need in correlation with the sleep homeostatic response. This correlation requires control of extracellular Ado acting on

neuronal ADORA1s to evoke the rebound SWA during SWS. SWS itself may be seen in this context as a gate allowing expression of SWA. The amplitude of the expression of homeostatic SWA is mediated by Ado.

Functional CNS targets of the homeostatic sleep response

The SWA homeostatic sleep response suggests the importance of SWS function. SWS is permissive to the expression of SWA which may be directly involved in sleep function as a means of rhythmically, increasing intracellular calcium. Calcium is a well-known intracellular signal messenger for activity-dependent gene expression. Sleep deprivation induces extensive changes in gene expression that recover during sleep as observed by transcriptome analysis employing microarrays (28, 29). The increase of expression of a panel of activity-activated genes including *Homer1a, NR4A1, Arc, cFos, Bib, Bdnf* and *Hsp27* directly correlates with the level of arousal. The method of sleep deprivation can determine the level of arousal. We have reported that sleep deprivation induced by cage change results in higher arousal than gentle handling (27). The panel of activity-activated gene expression varied in correlation with arousal level as elicited by either cage change or gentle handling. *Glut1* was increased to a similar extent by either method of sleep deprivation (27). All of the waking induced changes in gene transcript expression, observed during waking, resolved during sleep (28, 29) although the mechanism(s) responsible for the resolution, beyond the increase of Ado during wake and sleep deprivation and its decrease during sleep, remain speculative.

The synaptic changes brought on by sleep deprivation and the sleep homeostatic response are just beginning to be understood. Some provocative hints that a generalized down regulation of excitatory synapse strength in the cortex is associated with sleep are starting to emerge (30). A net increase in cortical synaptic strength due to plasticity-dependent processes, occurring in response to waking experience has been proposed (30). This may result in an increased metabolic demand leading to an overall downregulation synaptic strength during sleep. A recent study provided electron microscopy based evidence for sleep induced reduction of pre- and post-synaptic surface area consistent with this hypothesis, known as the Synaptic Homeostasis Hypothesis or “SHY” (31).

Ado is a likely mediator to transform metabolic demand to sleep need as it is under the control of glial Adk (6). The metabolic state of glia, sensed by glial Adk, influences the resolution of sleep need by affecting the rate of Ado metabolism. The rate of Ado metabolism in turn, controls the rate of decay of SWA during NREM sleep. Following sleep deprivation, when sleep need is high, the rate of SWA decay during NREM sleep is slowed, allowing greater expression of SWA and possibly, a more effective resolution of sleep need.

Notably, it was recently observed that Ado, by activation of ADORA1 can cause an increase, in the synaptic post-synaptic density (PSD), of HOMER1a (14). A similar increase in HOMER1a in the PSD was also observed in this study following sleep deprivation in association with increased Ado (21). Further, the transcript for Homer1a shows increased expression with sleep deprivation (32) and with direct activation of ADORA1 (33) and, finally, HOMER1a is required for activity-dependent homeostatic down-scaling of synaptic

strength (34). Accordingly, a pathway driven by sufficient waking to increase sleep need, increases extracellular Ado that acts at ADORA1s. The extracellular Ado increases expression of HOMER1a in the PSD during SWS to down-scale glutamatergic cortical synapses and it is reduced by glial metabolic-state-sensitive Adk resolving the need for sleep.

The signaling pathways upstream of Homer1a and activated by Ado, remain to be characterized. It seems likely that an integrated network(s) with multiple nodes controlling gene expression interacts with time spent in different behavioral states. Pharmacological antagonists in primary neuronal cultures implicate a necessary role for Gi, PLC and ERK signaling pathways (33) but their sufficiency for a sleep-dependent role has not been established. The role of Ado in the homeostatic sleep response is consistent with a metabolically related drive for this sleep function and it would be surprising if the only target of this metabolic drive was glutamatergic synaptic strength. Although glial metabolic control of synaptic strength is of central importance it seems likely that other aspects of sleep related homeostasis may eventually be characterized. A recent forward genetic screen for sleep genes has implicated a gene encoding a protein kinase, *Sik3* by showing a gain of function mutant, named “sleepy” (the mutation is a loss of one of the exons of *Sik3*) causes a constant state of sleep need in mice (35). This suggests that a sleep-need related gene network extending beyond the ADORA1-HOMER1a signaling pathway clearly warrants further examination.

The importance of understanding the function of such a potentially complex molecular network should not be underestimated by sleep’s modulatory nature. Although acute or chronic sleep disruptions are not immediately lethal, the functions modulated by sleep are vital to normal brain function. A healthy life requires rhythmic changes of CNS state from wake to sleep and back again.

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Highlights

1. SWA of SWS marks both the buildup and resolution of sleep need
2. This SWA buildup is caused by adenosine mediated facilitation of SWA by A1 receptor activation
3. The SWA decay is controlled by glial adenosine kinase
4. The velocity of adenosine metabolism by adenosine kinase is determined by glial ATP/[ADP*AMP]
5. Glial metabolic state by affecting adenosine metabolism modulates the sleep homeostatic response by controlling the rate of resolution of sleep need

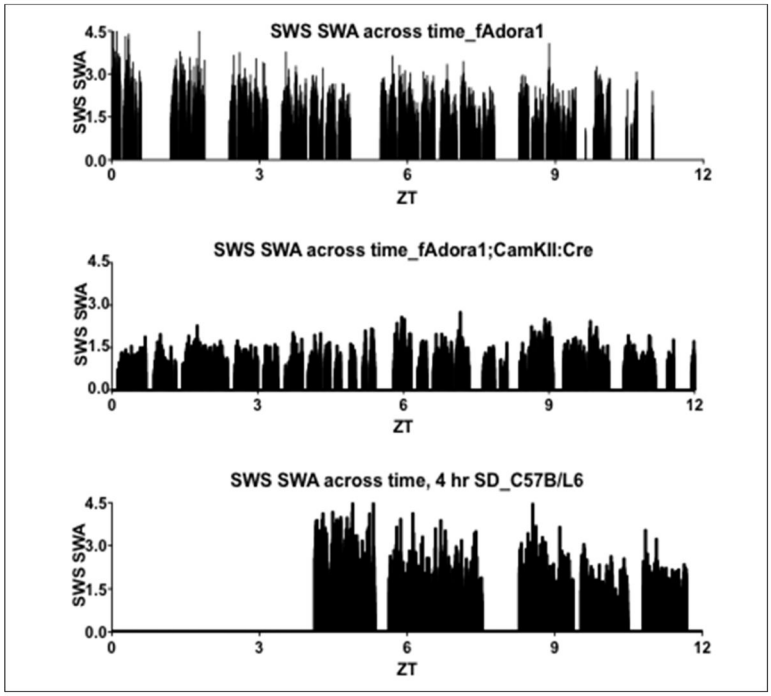

Figure 1.

The sleep phase from ZT=0–12 is shown. The Y axis shows normalized SWA during SWS. Top row is from a floxed Adora1 (wildtype, no exposure to Cre), the middle row is from an Adora1 mutant (floxed Adora1 x CamKII:Cre+) and the bottom row is from a C57BL/6 mouse in which sleep was deprived during the first 4 hours of the light phase. The Adora1 mutant is notable for its lack of decay of SWA across the sleep phase.

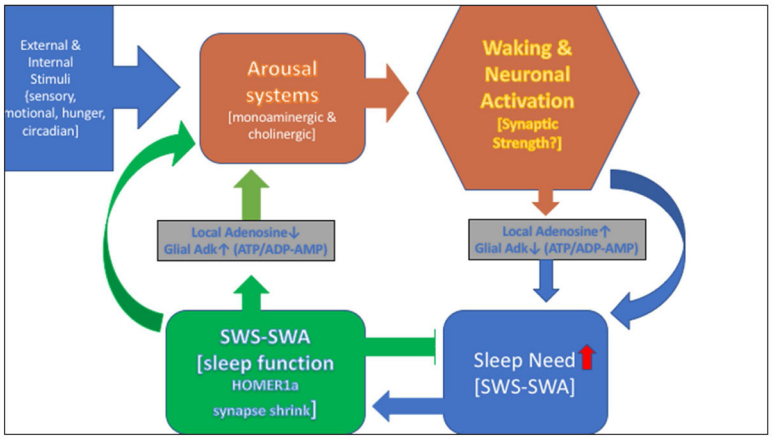

Figure 2.
Cartoon of relationship between Arousal, Waking and Sleep