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## Sleep and immune function: glial contributions and consequences of aging

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### Abstract

The reciprocal interactions between sleep and immune function are well-studied. Insufficient sleep induces innate immune responses as evidenced by increased expression of pro-inflammatory mediators in the brain and periphery. Conversely, immune challenges upregulate immunomodulator expression, which alters central nervous system-mediated processes and behaviors, including sleep. Recent studies indicate that glial cells, namely microglia and astrocytes, are active contributors to sleep and immune system interactions. Evidence suggests glial regulation of these interactions is mediated, in part, by adenosine and adenosine 5 - triphosphate actions at purinergic type 1 and type 2 receptors. Furthermore, microglia and astrocytes may modulate declines in sleep-wake behavior and immunity observed in aging.

### Introduction

Chronic insufficient sleep is associated with inflammation, metabolic syndrome, cardiovascular disease, increased sensitivity and to pain stimuli, fatigue, excessive daytime sleepiness, and impaired cognitive and physical performance. Symptoms of these pathologies are associated with increased levels of endogenous pro-inflammatory cytokines such as interleukin-1 (IL-1 ) and tumor necrosis factor (TNF ), and can be experimentally elicited by peripheral or central exogenous administration of these cytokines to subjects [1,2]. Conversely, inhibition of IL-1 or TNF attenuates many sleep-loss associated symptoms. Additionally, reduction of endogenous levels of IL-1 or TNF , whether in mutant mice or by use of soluble receptors, antibodies, or receptor antagonists,

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inhibits spontaneous sleep (reviewed [2], [3], and [4]). There is a wealth of evidence indicating that IL-1 and TNF are also involved in physiological sleep regulation and that their amplification during pathology is causative of characteristic sleep disturbances associated with many pathological states [2-4]. Indeed, the brain, including regions associated with the regulation of sleep-wake behavior, produces and is responsive to cytokines [2,3,5]. Furthermore, neuronal activity upregulates these cytokines in brain regions implicated in the regulation of sleep [6,7]. Impaired sleep also affects adaptive immune responses. Sleep deprivation attenuates antibody responses to vaccine [8,9], whereas good sleep imparts long-lasting immunoenhancing effects [10,11]. Furthermore, sleep is a profound regulator of cellular immunity and formation of immunological memory critical for adaptive responses to immune challenges (reviewed by [11]).

We acquired substantial insight into sleep and immune system interactions during the last 30 years. However, the cellular substrates for these interactions are less well understood. Understanding the role of glia in sleep and immune system functioning is crucial because research has started to shift the traditional view of these cells as passive constituents of the central nervous system (CNS) to active contributors capable of mediating behavior (see below). Furthermore, because the aforementioned inflammatory pathologies are common in elderly individuals, identifying age-related changes in glial cell functioning may be critical in elucidating the mechanisms driving senescence of sleep and immune networks in aging. This review highlights recent findings implicating a role for glia in sleep and immune interactions and aging.

## Microglia in sleep and immune function

Microglia are the resident immune cells of the CNS that are mobilized and activated in response to an immune challenge. The role of microglia in mediating responses to immune challenge has been studied exhaustively. Microglial influences on sleep-wake behavior are not extensively studied although recent data implicate microglia in sleep regulation. Microglia assume a deramified morphology, a marker of activation, in response to sleep deprivation [12]. In addition, slow wave activity is reduced following administration of minocycline, an inhibitor of microglial activation [13]. Minocycline inhibits microglial production of immunomodulators including cytokines and nitric oxide [13]. Intraperitoneal minocycline administration induces an acute increase in wakefulness and significantly reduces non-rapid eye movement sleep (NREMS) compared to saline-treated mice [14•]. Furthermore, minocycline inhibits sleep deprivation-induced augmentation of NREMS delta power, a surrogate indicator of sleep depth [14•]. Although data are limited, recent studies indicate microglia are potentially critical components of sleep regulatory mechanisms.

A possible effector of microglial influences on sleep-wake behavior may be extracellular adenosine-5 -triphosphate (ATP) acting at the purinergic type 2 receptor P2X<sub>7</sub> (P2X<sub>7</sub>R). The P2X<sub>7</sub>R links increased cellular activity during waking to adenosine and cytokine sleep modulation. Activation of glial P2X<sub>7</sub>R by extracellular ATP mediates post-translational processing of sleep regulatory substances including IL-1, TNF, and IL-6 [3,15,16]. P2X<sub>7</sub>R expression in brain is most prominent on microglia [15,16], and neurons and glia release ATP into the extracellular space in response to cellular activity [3]. Administration of P2X<sub>7</sub>R agonists increases time spent in NREMS and enhances electroencephalographic (EEG) delta power [17]. Conversely, P2X<sub>7</sub>R inhibition reduces NREMS in rats [17]. Furthermore, mice lacking the P2X<sub>7</sub>R exhibit less robust increases in NREMS and EEG delta power in response to sleep deprivation compared to wild type animals [17]. Collectively, the data suggest a role for microglia and purinergic receptors as one component of systems and networks that mediate sleep and immune interactions (Figure 1).

## Astrocytes in sleep and immune function

A traditional view of astrocytes was that they played a passive, supportive role for neurons. However, recent studies demonstrate that these cells are active contributors to complex behaviors and immune responses. Astrocytes are the most abundant glial cell type in the brain, respond rapidly to inflammation, express receptors for immunomodulators, and produce sleep regulatory substances in response to immune challenge [18,19]. Selectively inhibiting astrocyte gliotransmission via the dominant negative (dnSNARE) mouse reduces EEG slow wave activity during NREMS, a traditional measure of sleep pressure [20]<sup>1</sup>. Inhibition of vesicular release from astrocytes also attenuates the increase of NREMS and cognitive deficits typically observed subsequent to 6 h of sleep deprivation [20]. These data suggest astrocytic gliotransmission contributes to the modulation of sleep need.

Because altered gliotransmission of astrocytes results in reduced sleep pressure, studies have turned to astrocyte-derived adenosine, an ATP metabolite, as a potential molecular substrate of this effect. Adenosine accumulates in brain with increasing time awake [22••], and extracellular elevation of adenosine concentrations is astrocyte dependent [22••,23]. Indeed, inhibition of the adenosine 1 receptor (A<sub>1</sub>R) in wild type mice recapitulates the reductions of baseline EEG slow wave activity and responses to sleep deprivation observed in gliotransmission-impaired dnSNARE mice [20,24]. Conditional CNS A<sub>1</sub>R knockout mice also fail to demonstrate enhanced EEG delta power following intermittent sleep deprivation [25]. Conversely, mice lacking CD73, an ectonucleotidase that converts extracellular ATP to adenosine, have more spontaneous NREMS than wild type controls [26•]. Consistent with the notion that the A<sub>1</sub>R mediates sleep need, chronic sleep restriction increases A<sub>1</sub>R mRNA expression in the wake-promoting basal forebrain in rats [27] although not in the sleep-promoting hypothalamus of mice [26•].

In response to immune challenge, A<sub>1</sub>R activity is upregulated to impart neuroprotection via generating neurotrophic factors, downregulating excitotoxicity, preventing excessive astrogliosis, and inhibiting pro-inflammatory cytokines [28-31]. Blockade of this receptor increases hippocampal injury in response to hypoxia [32] and mortality to infectious disease [33]. Furthermore, lipopolysaccharide (LPS)-induced elevations of EEG slow wave activity are attenuated in gliotransmission-impaired dnSNARE mice, an effect mimicked by central inhibition of the A<sub>1</sub>R in wild type mice [34••]. Although, studies regarding the impact of inhibiting the A<sub>1</sub>R or gliotransmission on sleep-immune interactions are generally lacking, current data suggest astroglial modulation of sleep and immune function is mediated, in part, by astrocyte-derived ATP and/or adenosine and subsequent activation of purine type 1 and 2 receptors (Figure 1).

## Sleep, immune function, and aging

Sleep alterations are a well-documented feature of aging. Sleep in old age is characterized by more fragmentation, less rapid eye movement sleep (REMS), reduced time in deeper stages of NREMS (i.e. stages N2 and N3), decreased EEG delta power, and more time spent in lighter stages of NREMS which results in more nighttime awakenings. Furthermore, sleep onset is progressively earlier and is accompanied by early morning wake time and more frequent daytime napping (for review see [35] and [36]). Although healthy aging need not be associated with sleep complaints, the elderly frequently indicate they have difficulty initiating or maintaining sleep [37]. Increased severity of these alterations in sleep can

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<sup>1</sup>EEG slow wave activity is regulated independently from duration of NREMS [21]. There is good evidence for the involvement of extracellular adenosine in its regulation; this might occur via vasodilation induced by adenosine since cerebral blood flow alters EEG slow wave power.

increase susceptibility to disease and predict age-related disease onset [38,39]. Indeed, several brain regions associated with sleep-wake behavior are impacted by neurodegenerative disease [35].

Poor sleep can also exacerbate the age-related changes in immune system functioning. “Inflammaging” is the term used to describe the homeostatic shift to a chronic, low-grade inflammatory state in aged individuals [40]. This change is manifest by increased inflammatory mediators centrally and peripherally [41], enhanced production of reactive oxygen and nitrogen species [42], as well as suppression of anti-inflammatory mediators and antioxidants [43]. A similar syndrome is elicited by chronic sleep loss in younger subjects. This shift predisposes one to exacerbated responses to immune challenge compared to that of normal, younger individuals. Indeed, the severity of this low-grade inflammatory state is predictive of all-cause mortality in the elderly [44]. Alternatively, longevity is inversely correlated with plasma concentrations of IL-6 [45], a mediator of chronic inflammation in aging [46]. Inflammation is also implicated in contributing to poor sleep observed in the elderly. However, recent data demonstrate that moderate exercise decreases pro-inflammatory cytokines IL-1 and TNF and increases the anti-inflammatory cytokine IL-10 in aged individuals [47•,48•]. This effect is associated with improved sleep maintenance and enhanced quality of life [47•]. Exercise also increases circulating concentrations of neurotrophic factors which are associated with increased temporal lobe connectivity indicative of improved neurocognition [49]. Lastly, better sleep efficiency is associated with lower concentrations of IL-6 in elderly women [50].

Although poor sleep in aged individuals increases immunomodulators and, likewise, inflammation alters sleep, the dynamics differ from those observed in younger counterparts. For example, pre-clinical data demonstrate that intracerebroventricular administration of IL-1 reduces REMS to a similar extent in aged and middle-aged rats. However, in aged rats, there is no observed increase in NREMS characteristic of IL-1 challenge in younger animals [51]. These data indicate a potential dysregulation of interactions between sleep and immune networks in aging. Furthermore, the lack of NREMS response may contribute to increased morbidity and mortality in response to immune challenge in the elderly [52]. Studies regarding the cumulative effects of aging on sleep and immune function are generally lacking. However, understanding these interactions is increasingly important with the rapid growth of the 65 years and older population.

## Glial contributions to aging

Age-related changes of the CNS are not attributed to neuronal loss per se, but are a consequence of synaptic alterations, which may be due to decreased synaptic contacts (reduced dendritic spines) or molecular alterations of intact synapses [53]. With age, there is a progressive decline in gene expression relating to vesicular function, receptor trafficking, post-synaptic density scaffolding, and neurotrophic systems [54]. Glia are strong candidates for effectors of age-related alterations in sleep and immune function as these cells are known mediators of synaptic homeostasis [55]. One of the characteristics of aging is a morphological shift of microglia and astrocytes to a primed or activated state [40,56]. Excessive and prolonged production of pro-inflammatory cytokines in aged CNS in response to systemic immune challenge with LPS is a result of primed microglia [57,58]. Also, P2X<sub>7</sub>R expression increases with age in mouse brain, an effect associated with damage to the post-synaptic density [59••]. Furthermore, astrocytes become hypersensitive after exposure to microglial-conditioned media, which may perpetuate the chronic inflammatory state in aging [60•]. Aging brain is associated with increased astrogliosis [57], and astrocytes produce 10-fold more IL-6 in aged patients relative to younger counterparts [61•]. Interestingly, peripheral concentrations of cytokines do not necessarily reflect

neuroinflammatory states [57]. Collectively, these data suggest that aging may be a centrally mediated process driven by glial alterations of the CNS milieu.

## Conclusions

Reciprocal influences between sleep and immune system are well-documented, but the cellular and molecular substrates modulating in these interactions are not completely understood. Current data demonstrating glial contributions to sleep regulation suggests further investigation is warranted as these cells may be critical mechanistic components of sleep and immune interactions throughout the lifespan. Future studies might aim to address the immune consequences of inhibiting glial activity and how this relates to sleep alterations. Also, the mechanisms driving dysregulation of sleep and central immune responses in aging are not well defined. Answering these, and other questions, is necessary before network components of sleep-immune interactions and their role in healthy aging may be fully elucidated.

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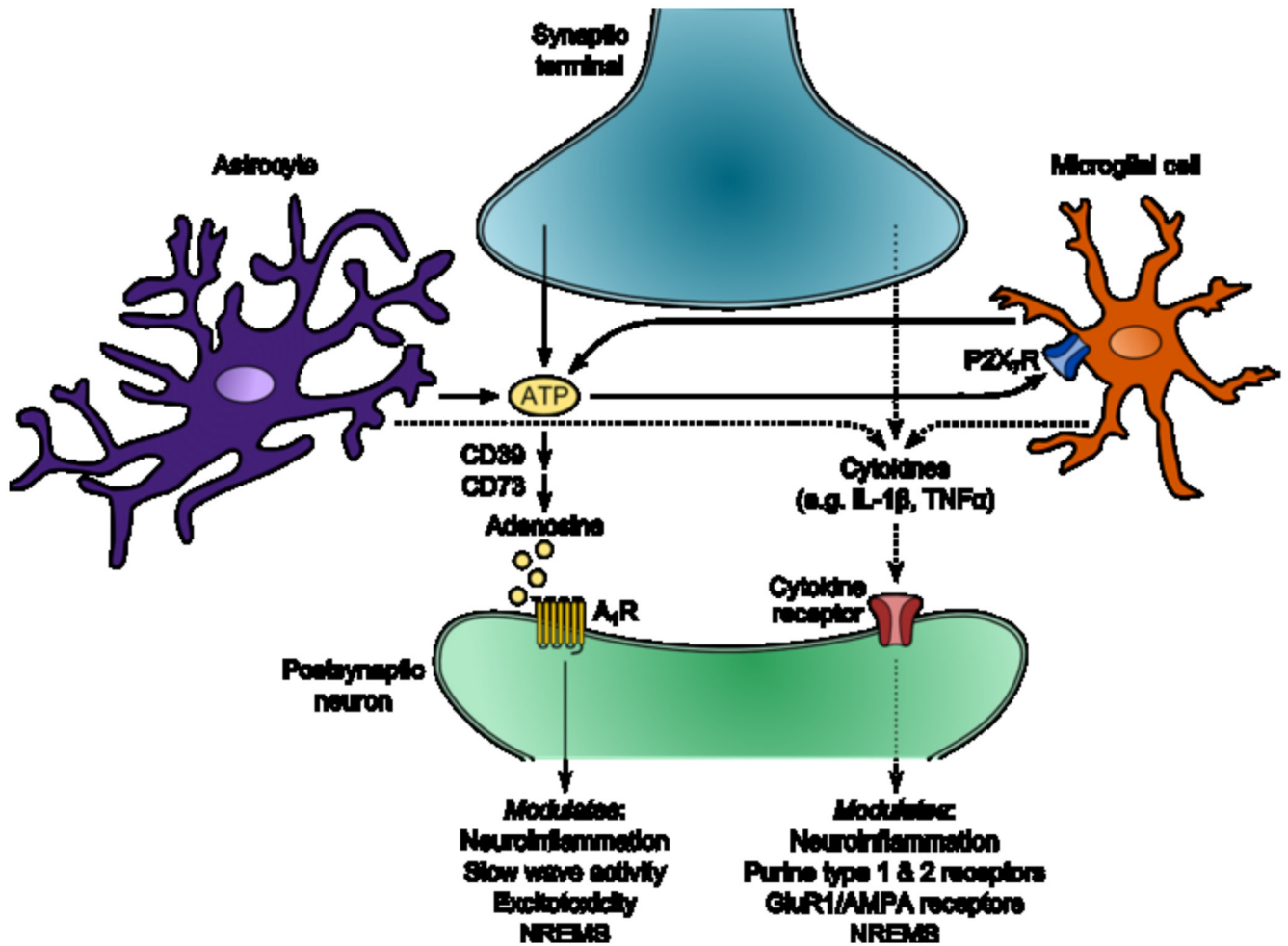
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### Highlights

- Microglia modulate NREMS and slow wave activity via production of immunomodulators.
- Astrocytic gliotransmission mediates NREMS and sleep pressure.
- ATP (via P2X<sub>7</sub>R) and adenosine (via A<sub>1</sub>R) may be effectors of glial sleep regulation.
- Aging is associated with poor sleep quality and chronic, low-grade inflammation.
- Primed microglia and activated astrocytes contribute to changes of the aging CNS.



**Figure 1.**

Glial modulation of sleep and immune interactions. Cellular activity causes ATP release into the extracellular space via neurotransmission and gliotransmission. Extracellular ATP induces rapid effects once metabolized to adenosine by ectonucleotidases such as CD39 and CD73. Adenosine binds to purine type 1 receptors like the A<sub>1</sub>R to modulate EEG slow wave activity and NREMS, as well as local neuroinflammation and excitotoxicity. Slower effects of extracellular ATP occur through direct activation of purine type 2 receptors such as the P2X<sub>7</sub>R prominently expressed on microglia. P2X<sub>7</sub>R activation induces processing and release of cytokines including, but not limited to, IL-1 and TNF. Cytokines subsequently act on their respective receptors to activate transcription factors like nuclear factor- $\kappa$ B (not shown) which modulates neuroinflammation, physiological and pathological sleep, and gene transcription of receptors such as the A<sub>1</sub>R, AMPA, and the AMPA subunit GluR1. This overly simplified schematic focuses on the featured topics of this mini-review, and thus, not all cellular and molecular components are fully represented. AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; GluR1, glutamate receptor 1.