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Sleep and immune function: glial contributions and consequences of aging

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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.

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Introduction

Chronic insufficient sleep is associated with inflammation, metabolic syndrome, cardiovascular disease, increased sensitivity 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 β (IL-1 β) and tumor necrosis factor α (TNF α), and can be experimentally elicited by peripheral or central exogenous administration of these cytokines to subjects [1,2]. Conversely, inhibition

of IL-1 β or TNF α attenuates many sleep-loss associated symptoms. In addition, reduction of endogenous levels of IL-1 β or TNF α , whether in mutant mice or by use of soluble receptors, antibodies, or receptor antagonists, inhibits spontaneous sleep (reviewed [2–4]). There is a wealth of evidence indicating that IL-1 β and TNF α 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 P2X₇ (P2X₇R). The P2X₇R links increased cellular activity during waking to adenosine and cytokine sleep modulation. Activation of glial P2X₇R by extracellular ATP mediates post-translational processing of sleep regulatory substances including IL-1 β , TNF α , and IL-6 [3,15,16]. P2X₇R 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 P2X₇R agonists increases time spent in NREMS and enhances electroencephalographic (EEG) delta power [17]. Conversely, P2X₇R inhibition reduces NREMS in rats [17]. Furthermore, mice lacking the P2X₇R exhibit less robust increases in NREMS and EEG delta power in response to sleep deprivation as 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 SNARE (dnSNARE) mouse reduces EEG slow wave activity during NREMS, a traditional measure of sleep pressure [20].¹ Inhibition of vesicular release from astrocytes also attenuates the increase of NREMS and cognitive deficits typically observed subsequent to 6 hours of sleep deprivation [20]. These data

¹ 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.

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 (A₁R) 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 A₁R 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 A₁R mediates sleep need, chronic sleep restriction increases A₁R 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, A₁R 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 A₁R in wild type mice [34**]. Although studies regarding the impact of inhibiting the A₁R or gliotransmission on sleep–immune interactions are generally lacking, current data suggest that 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 [35,36]). 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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