

Sleep and innate immunity

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1. ABSTRACT

Many pro-inflammatory molecules, such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha) are somnogenic, while many anti-inflammatory molecules inhibit sleep. Sleep loss increases the production/release of these sleep regulatory pro-inflammatory molecules. Further, sleep changes occurring during various pathologies are mediated by these inflammatory substances in response to pathogen recognition and subsequent inflammatory cellular pathways. This review summarizes information and concepts regarding inflammatory mechanisms of the innate immune system that mediate sleep. Further, we discuss sleep-immune interactions in regards to sleep in general, pathologies, and sleep as a local phenomenon including the central role that extracellular ATP plays in the initiation of sleep.

2. INTRODUCTION

Sleep is vital to many biological activities including host responses to pathogens (1). Inflammation is an immunological process triggered by a variety of self or non-self stimuli, including pathogens, irritants, cellular damage or dysregulation, local brain use, and waking activity (2). Sleep and the immune system are highly conserved between animals from flies to humans. In fact, homologous genes for many sleep and immune-associated genes are found in mice and even invertebrates such as *D. Melanogaster* and *C. Elegans* (3). Inflammation modulates sleep and the effects of sleep loss and conversely sleep or sleep loss alters inflammatory responses including the production of inflammatory regulatory substances activated by neuronal /glial use and immunologic pathogen recognition (1).

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Table 1. Criterion for sleep regulatory substance.

Criterion For Sleep Regulatory Substance
In the brain, these sleep regulatory substances and/or their receptors oscillate with sleep/wake proclivity.
Sleep increases or decreases when sleep regulatory substances are injected locally into the central nervous system or systemically.
The inhibition or removal of sleep regulatory substances changes sleep.
Sleep is altered by sleep regulatory substances in response to pathogens.

3. INFLAMMATION

Inflammatory mechanisms operate over various time scales from seconds to days. These mechanisms alter many physiological and pathological functions including blood flow, cellular mediators, cell migration, and sleep (2). Primary sleep disorders, such as insomnia and obstructive sleep apnea, are associated with dysregulated inflammatory mechanisms (4). Persistent inflammation is also associated with many diseases, such as Type 2 diabetes (5), cardiovascular disease (6), colorectal cancer (7), inflammatory bowel disease (8), and asthma (9). Interestingly, chronic short sleep duration is also associated with inflammatory diseases including cardiovascular disease (10), Type 2 diabetes, and cancer (11). Moreover, pathogens including influenza, bacteria, and human immunodeficiency virus (HIV) alter sleep, in part, through inflammatory mechanisms (12).

In 1909, Kuniomi Ishimori published his findings that cerebral spinal fluid transferred from sleep deprived dogs into control dogs increased sleep in the recipients (13). This finding was confirmed independently by Henri Pieron soon after (14). These findings suggested that sleep regulatory substances are produced as a consequence of waking activity. Subsequently, most characterized sleep regulatory substances have been shown to directly or indirectly modulate inflammation (1). There are criteria that a molecule must meet to be considered a sleep regulatory substance (Table 1). Many molecules and their associated receptors, metabolites, micro RNAs, transcription factors, etc, have the capacity to alter sleep. Yet, only a few sleep regulatory substances have *met all* the criteria. They include interleukin-1beta (IL-1 beta), tumor necrosis-alpha (TNF-alpha), and growth hormone-releasing hormone (GHRH) for non-rapid eye movement (NREM) sleep, and prolactin and nitric oxide (NO) for rapid-eye movement (REM).

4. GLIA

There is much evidence that glia play a significant role in sleep. Glia comprise approximately 90% of brain cells. Glia produce many humoral regulators of inflammation and sleep. Glia interaction with neurons is quite extraordinary, as they serve to clear neurotransmitters from synaptic clefts with membrane transporters, release many molecules such as cytokines, adenosine triphosphate (ATP), and adenosine that modulate inflammation and

neuronal function, release neurotransmitters, and alter the local ionic environment (15). Glia including microglia, astrocytes, oligodendrocytes, and Schwann cells contain many of the same ligand-gated ion channels as neurons including GABA and glutamate receptors. Under cell culture conditions certain glia, such as astrocytes and oligodendrocytes, produce action potentials mediated by voltage-gated outward potassium currents (16, 17). However, it is debatable if this occurs *in vivo*. Thus, glia, through autocrine and paracrine mechanisms modulate inflammation, and as a consequence of their electrical actions likely are a key component in the genesis of sleep and the electroencephalogram.

5. CYTOKINES

Protein, peptide, or glycoprotein molecules that signal inflammatory pathways through autocrine, paracrine, and/or endocrine mechanisms are termed cytokines (2). Neurons, glia, and a wide diversity of other cell types produce cytokines. Cytokines induce their effect at very low levels, such as pico or femtomolar concentrations. They induce pro- or anti-inflammatory responses. Cytokines, such as IL-1 beta or TNF-alpha, also modulate memory (18), performance, appetite (19) cognition (20), pain (21), fatigue (22), sleepiness (1), and sleep. IL-1 beta, TNF-alpha, and interleukin-6 (IL-6) are well-characterized pro-inflammatory somnogenic cytokines (1). However, many other cytokines are somnogenic or anti-somnogenic. Further, cytokines, such as IL-1 beta and TNF-alpha, alter expression of circadian genes including altering E-box regulatory elements activation through CLOCK-BMAL (23, 24). Cytokines are integral to sleep homeostat regulation (Figure 1).

5.1. Interleukin-1

In 1984, IL-1beta was the first cytokine implicated in sleep regulation (25). IL-1beta is one of 11 family members with respective receptors termed the interleukin-1 family (IL1F) (26). The pro-inflammatory IL1F members, IL-1 beta, interleukin-1alpha (IL-1alpha), and interleukin-18 (IL-18) promote NREM sleep, while the anti-inflammatory IL1F member interleukin-1 receptor antagonist (IL-1RA) reduces NREM sleep (1). IL-1beta was first identified as an endogenous pyrogen (27), although it also functions to regulate immunity, inflammation, hyperalgesia, hematopoiesis, and central nervous system (CNS) processes such as sleep (26). IL-1beta and its receptors (interleukin-1 Type 1 and interleukin-1 Type 2) are propagated by a variety of cells within the CNS including neurons, astrocytes, macrophages, and microglia. The interleukin-1 Type 1 receptor is linked to pro-inflammatory actions. The interleukin-1 Type 2 receptor because it lacks an intracellular signaling domain competitively inhibits IL-1beta binding to the interleukin Type 1 receptor, thus inhibiting inflammation. Further, the IL-1RA competitively inhibits IL-1beta from binding to interleukin-1 Type 1 and Type 2 receptors resulting in anti-inflammatory reactions. Upon receptor activation, IL-1beta triggers many inflammatory cellular pathways including nuclear factor-kappa B (NF-kappaB), cyclooxygenase (COX),

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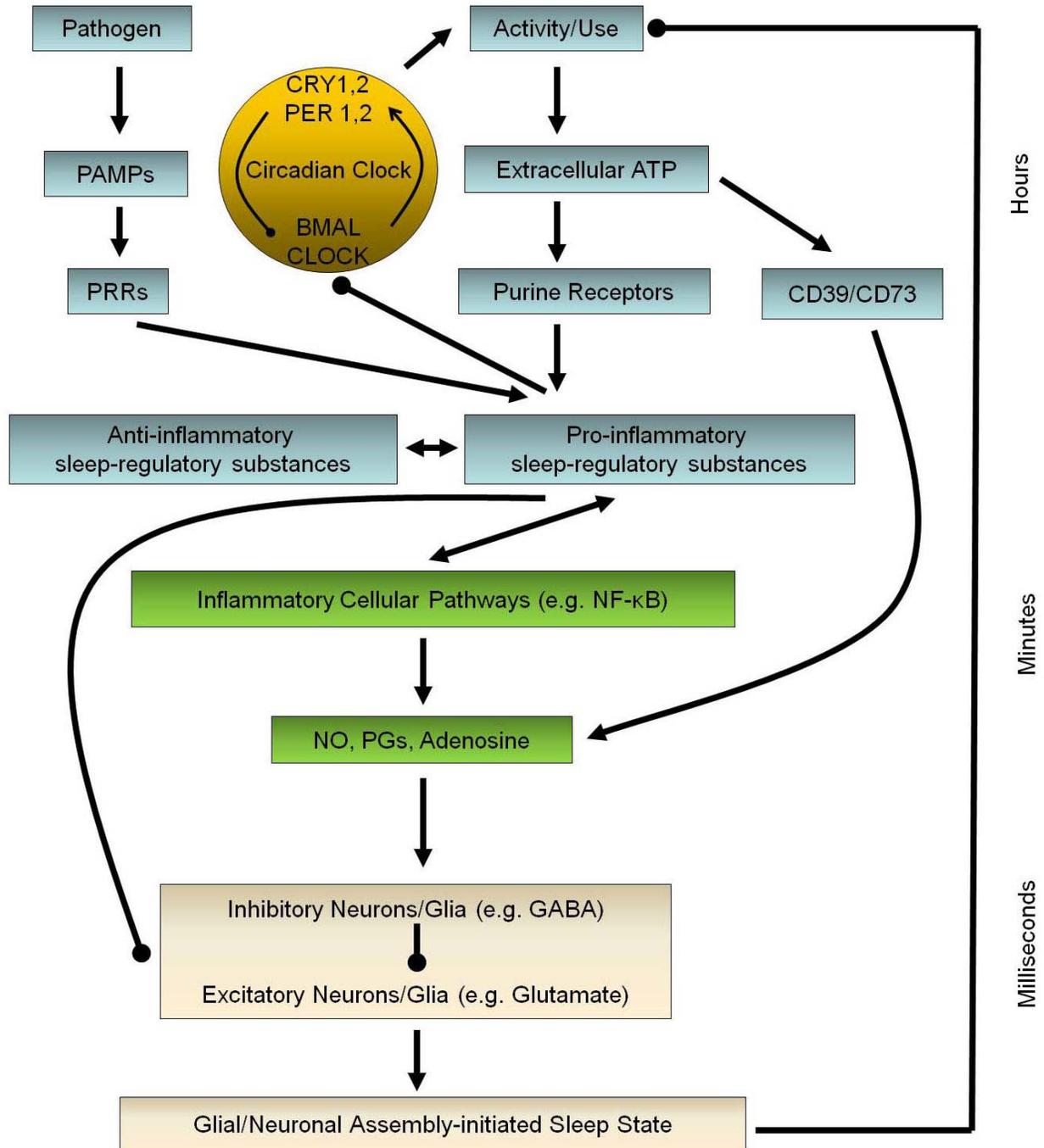


Figure 1. Sleep homeostat.

prostaglandin E₂ (PGE₂), mitogen-activated pathogen kinase (MAPK), and inducible nitric oxide synthase (iNOS).

Circadian fluctuations in IL-1beta and IL-18 expression occur in various brain areas coinciding with the sleep/wake cycle and sleep propensity (1). Systemic or central administration of IL-1beta enhances NREM sleep for hours. The IL-1RA inhibits IL-1beta induced NREM

sleep in rats and rabbits when applied intraperitoneally or intraventricularly. IL-18 also enhances NREM sleep duration following systemic administration. Somnogenic doses of IL-1beta and IL-18 administration can attenuate REM sleep. Lower somnogenic doses of IL-1beta promote NREM sleep duration without affecting REM sleep. In contrast, high doses of IL-1beta inhibit both NREM and REM sleep. The IL-1RA does not alter REM sleep.

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Increased EEG delta power occurring during NREM sleep is a classic measure of sleep intensity; e.g. EEG delta power during NREM sleep is high at the threshold of sleep induction (1). Both systemic and central IL-1beta administration enhances NREM sleep EEG delta power. Inhibiting IL-1beta with antibodies or pharmaceuticals reduces spontaneous NREM sleep and EEG delta power. Moreover, the enhanced NREM sleep and EEG delta power following sleep deprivation are attenuated with IL-1beta antibodies. Compared to control mice, mice lacking the interleukin Type 1 receptors have reduced NREM sleep and REM sleep during the active dark cycle but have normal sleep durations during most of the light cycle. Further, IL-1beta levels in response to certain pathologies, such as influenza, are associated with increases in NREM sleep duration and EEG delta power (12). IL-1beta effects on sleep duration and EEG delta power are found in multiple species suggesting an ancient link between inflammation and sleep regulation.

5.2. Tumor Necrosis Factor

The somnogenic actions of TNF-alpha were first published in 1987 (28). The TNF family is quite large with more than 40 ligand-receptor pairs (29). However, TNF-alpha is the most stringently investigated member of this family. TNF-alpha was discovered as an endotoxin-induced serum factor causing the necrosis of tumors and later as an endogenous pyrogen. Thereafter, TNF-alpha was shown to mediate inflammation, apoptosis, septic shock, viral replication, neuroprotection/neurotoxicity, appetite, and sleep. TNF-alpha and its receptor tumor necrosis factor receptor 1 (TNFR1: 55 kD receptor) are produced by various CNS cell types including neurons, glia, and macrophages, while the other receptor for TNF-alpha, tumor necrosis factor receptor 2 (TNFR2), is found primarily on immunocytes. TNF-alpha is involved in activating many inflammatory cellular pathways, including NF-kappaB.

Wakefulness enhances TNF-alpha protein levels and expression in the brain (1). Thus, following sleep deprivation TNF-alpha expression is elevated. Further, the highest brain levels in rats occur at the onset of light, a period of maximal sleep propensity. Systemic or central administration of TNF-alpha enhances NREM sleep duration and EEG delta power during NREM sleep. This effect occurs in all species that have been investigated. REM sleep is suppressed following TNF-alpha administration but only at high doses. Further, NREM sleep duration in response to muramyl dipeptide (which increases NREM sleep duration) is inhibited when rabbits are given a TNF-alpha inhibitor (a biologically active fragment of the soluble tumor necrosis factor 55 kDa receptor) (12). Mice lacking the TNFR1 have lower spontaneous NREM and REM sleep durations during the dark to light transition period compared to mice with intact receptors (1). Moreover, mice lacking the TNFR1 do not exhibit enhanced NREM sleep after TNF-alpha administration, although they remain responsive to IL-1beta. Mice that lack TNFR1 and TNFR2 have attenuated NREM sleep in the active dark cycle and more REM sleep in the inactive light cycle (30). Pathogen-induced NREM sleep, such as with

bacteria or influenza virus, is associated with increased TNF-alpha production (12).

A large literature indicates that circulating levels of TNF-alpha mediate sleep and sleepiness. Circulating TNF-alpha levels increase with sleep propensity (31). In humans, TNF-alpha levels are also increased in certain medical conditions associated with altered sleep including sleep apnea (32), fibromyalgia (33), insomnia (34), and obesity (35). Moreover, elevated circulating levels of TNF-alpha also occur with certain pathologies including influenza virus and trypanosome infections (36, 37). In rodents, elevated plasma TNF-alpha levels are associated with enhanced sleep following sleep deprivation (38). While the blood-brain barrier prevents the passage of many large molecules from the circulation to the brain, there are regions where molecules including TNF-alpha are transported across the barrier (39). Therefore, circulating pro-inflammatory cytokines, such as TNF-alpha, may be able to modulate brain inflammation and sleep by transversing this barrier. Systemic cytokines also signal the brain via vagal afferents (40, 41, 42).

6. INFLAMMATORY CELLULAR PATHWAYS

Sleep regulatory substances activate a number of inflammatory cellular pathways (1). These pathways in turn modulate sleep regulatory substances and sleep. In particular, IL-1beta and TNF-alpha are part of these inflammatory cellular pathways; they upregulate themselves as well as multiple other cytokines. NF-kappaB, NO, and COX inflammatory cellular pathways are implicated in sleep regulation; other cellular pathways exist that also alter sleep.

NF-kappaB is a transcription factor involved in cellular responses to cytokines, pathogens, neurotransmitters, and ATP (43). NF-kappaB is present in all nucleated cells including neurons and glia. Pro-inflammatory sleep regulatory substances, such as IL-1beta and TNF-alpha, are transcribed following NF-kappaB activation and nuclear localization (1). In contrast, anti-inflammatory anti-somnogenic sleep regulatory substances, such as IL-4 and IL-10, inhibit NF-kappaB activation. NF-kappaB exhibits a diurnal rhythm in the cortex and sleep deprivation activates cortical NF-kappaB (44). Further, inhibiting NF-kappaB activation reduces spontaneous NREM sleep. Nevertheless, mice lacking the NF-kappaB p50 subunit have enhanced spontaneous NREM and REM sleep (45). These mice respond to LPS with increased NREM and attenuated REM sleep. NF-kappaB activation is regulated by a number of molecules (i.e. p50, p65, relA, etc.) and it acts as an enhancer element for transcription of many pro- and anti-inflammatory molecules, which have the capacity to regulate sleep. Thus, NF-kappaB seems to be a key regulatory node in sleep regulation. However, the inflammatory-related interactions of this pathway with sleep have yet to be completely characterized.

Nitric oxide regulates physiological and immunological processes including vasodilatation, inflammation and sleep (46). Nitric oxide synthase (NOS)

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catalyzes the conversion of the nitrogen of arginine in the presence of nicotinamide adenine dinucleotide phosphate and dioxygen to NO. Many brain cells including macrophages, neutrophils, and microglia, produce inducible NOS (iNOS) and the brain specific neuronal NOS (nNOS). Brain iNOS has a circadian variation and increases with sleep propensity (47). In rats, iNOS increases during sleep deprivation. NREM and REM sleep are enhanced after administration of NO precursors, such as L-arginine, and other NO donors such as morpholinosydnonimine or SIN-1. Conversely, NREM and REM sleep are inhibited with iNOS inhibitors, such as N-nitro-L-arginine-methyl-ester and 7-nitro-indazole. iNOS knockout mice have reduced NREM sleep and enhanced REM sleep compared to wild type mice. This change is similar to that observed in TNF double receptor knockout mice; TNF-alpha mediates many of its actions via iNOS. In addition, mice lacking iNOS or nNOS have reduced NREM sleep in response to influenza challenge compared to mice possessing those genes (48). The sleep regulatory effect of NO is complex because many sleep regulatory substances including IL-1 beta, TNF-alpha alter NO, iNOS, and nNOS production.

The enzyme COX converts arachidonic acid to prostaglandin H₂; this is the rate limiting step in prostaglandin production (49). There are two separate COXs. COX-1 is constitutively expressed, while COX-2 is inducible. COX-2 modulates inflammation and sleep (1), and is found in most mammalian cells including macrophages, and microglia. Alternatively, inflammatory sleep regulatory substances including IL-1beta and TNF-alpha induce COX-2 expression (49). Inhibiting COX-2 attenuates spontaneous NREM and TNF-alpha-induced sleep (50, 51). Additionally, sleep is inhibited with the COX-1 and COX-2 inhibitor acetaminophen. Moreover, two downstream prostanoids, prostaglandin D₂ and prostaglandin E₂ are posited to be involved in sleep and wake regulation (52, 53), respectively.

7. PATHOGENS

Many pathogens, including bacteria influenza virus, and HIV are associated with altered sleep (12). The sleep regulatory substance Factor S isolated from human urine and rabbit brain was identified as muramyl peptide (54, 55). The structure of Factor S is similar to the monomeric muramyl peptides found in bacterial peptidoglycan. Subsequent research led to investigations of how pathogen-associated molecular patterns (PAMPs) and their respective pattern recognition receptors (PRRs) alter sleep (12). Intriguingly, pathogens altering sleep affect many of the same inflammatory cellular pathways, cytokines, and other sleep regulatory substances that waking activity does. It thus appears that the excessive sleep or sleepiness occurring with many infections is the consequence of amplification of physiological sleep regulator mechanisms.

The first description of the effects of a pathogen on sleep over the course of the induced acute phase response involved infecting rabbits with *Staphylococcus aureus* (56). *Staphylococcus aureus* infected rabbits exhibit

enhanced NREM sleep and less REM sleep. Similar sleep patterns were found with other pathogens including *Escherichia coli* and *Pasteurella multocida* (12). However, microbial-mediated sleep effects vary depending upon the species, route of infectious agent entry, time of day of exposure, and prior sleep history. In addition, bacterial cell wall components, such as the endotoxin lipopolysaccharide—a component of the outer membrane of gram-negative bacteria, enhance NREM sleep when injected systemically or centrally. Finally, high doses of heat-killed bacteria also have the capacity to induce sleep and other facets of the acute phase response, thereby suggesting that bacterial replication *per se* is not required for bacterial PAMP recognition by PRRs. These effects, like muramyl peptides, are also mediated by cytokines. Sleep alterations induced by these pathogens on their components are quite profound, similar to those sleep responses induced by central or systemic application of IL-1beta or TNF-alpha. Indeed, the IL-1RA and anti-IL-18 attenuate the enhanced NREM sleep induced by muramyl dipeptides indicating that pro-inflammatory cytokines are responsible for bacterial pathogens alteration of sleep.

The host's acute phase response to influenza viral infection involves many of the same responses induced by bacteria including increased sleep, fever (although mice exposed to influenza have reduced body temperature), and reduced activity (12). In humans, low titers of influenza only appear to alter sleep and not other acute phase responses. In mice and rabbits, the aforementioned acute phase response characteristics are observed with live but not killed influenza virus. However, the mechanisms for sleep-induced effects of influenza are not fully understood.

Influenza viral challenge is associated with IL-1beta, TNF-alpha, IL-6, and interferon production in the lung and brain and in mice sleep is enhanced for days during the infection (12). Mice lacking both TNF receptors have attenuated NREM sleep responses to influenza infection compared to mice that have intact receptors suggesting that TNF-signaling is required for the manifestation of the full acute phase response (30). Further, in response to influenza infection, mice lacking the iNOS gene (iNOS induction is downstream from TNF-alpha activation) have lower NREM sleep responses and greater REM sleep suppression compared to controls (48). Inflammatory sleep regulatory substances produced/regulated by glia mediate the acute phase sleep response to viral infection. For example, macrophages and microglia have the capacity to produce large amounts of IL-1beta and TNF-alpha in response to viral infection. Moreover, mice lacking macrophage inflammatory protein 1-alpha, which is involved with microglial regulation, do not have the typical dark phase enhanced sleep in response to influenza infection than wild types (57).

After intranasal influenza virus challenge, the virus is found in the olfactory bulb and is associated with increased pro-inflammatory cytokine production in the olfactory bulb (58). The virus is typically not detected in other brain regions such as the somatosensory cortex but has been reported in the hypothalamus (59). Nevertheless,

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in mice, the timing of the acute phase responses, including sleep alterations, correlates with virus localization to the lungs. Systemic inflammatory cytokines stimulate afferent vagal nerve inputs to promote sleep (40, 41, 42). Consequently, it is likely that the observed sleep effects following intranasal influenza inoculation involve inflammatory stimulation of vagal afferents.

One aspect of the immune response to viruses and its interaction with sleep involves antibody responses. For instance, in humans, acute sleep deprivation inhibits hepatitis A vaccine-generated antibodies (60). Further, a mild amount of sleep loss prior to immunization against influenza reduces immunoglobulin G antibodies to influenza for days, although this antibody titer difference disappears 3 weeks after immunization (61). Yet, in mice, mild amounts of sleep loss do not alter antibody development against influenza (62). Nonetheless, antibody protection and acute phase responses may interact to alter one another, although the mechanisms are mediated through different pathways. Thus, sleep alone is an insufficient measurement of influenza pathogenesis.

The effects of sleep loss on the host's response to influenza remain to be clarified. Prior sleep loss before inoculation is described as being protective while sleep loss following inoculation being detrimental. (63, 64, 65). Sleep loss alters inflammatory substances and the magnitude and direction of the effects are likely dependent on the activation state of these substances. For instance, the length and type of sleep deprivation, and the time of day affect the ability of inflammatory substances to interact with the host's response to the virus. In addition, the viral preparations used or the host's immunological status are likely key elements. Sleep deprivation prior to infection may be protective as similarly found in mice with B16 melanoma or *D. melanogaster* with bacteria resistance (66, 67). Consequently, it is plausible that sleep deprivation under certain circumstances can prime the immune system by altering inflammatory agents or pathways to enhance the immune response to a pathogen.

Viruses, such as HIV, also alter sleep. Sleep complaints and excessive daytime sleepiness, insomnia, and night time awakenings are common in HIV infected individuals (68). Further, disturbed sleep is magnified in these individuals as the disease progresses. A reduction in EEG slow wave activity is often found in individuals with HIV (69). However, individuals with HIV that do not show other typical symptoms associated with AIDS have enhanced slow wave sleep before acquired immune deficiency syndrome develops (70, 71). HIV infects microglia, and individuals with HIV have impaired macrophage and microglial functioning (72). Thus, impairment in these particular cells is likely to alter sleep regulatory substances which further alter sleep. Indeed, HIV is associated with impaired TNF-alpha release (73). Consequently, it is likely that individual with HIV have impaired abilities to mount the necessary daily sleep regulatory cytokine responses via microglia leading to their sleep disturbances and reduced EEG slow wave activity.

7.1. Pattern Recognition Receptors

Pathogens, including bacteria, flagellum, viruses, and their components including muramyl dipeptides, LPS, RNA, and DNA are pathogen-associated molecular patterns (PAMPs) (74). PAMPs are highly conserved molecular components of pathogens. Pathogenic components are recognized by pattern recognition receptors (PRRs) on or within certain cells. PAMPs play a vital role to the identification and processing of pathogens. Enhanced NREM sleep following muramyl dipeptide, LPS, gram negative and gram positive bacteria, viral RNA, and many other pathogens occur through the activation of PAMP receptors (12). PAMP receptors on the cell surface, endosome or within the cytosol include toll-like receptors (TLRs), and nucleotide binding oligomerization domain-like receptors (74). Upon PRR activation inflammatory pathways, including NF-kappaB, COX and NOS, activate inflammatory molecules, sleep regulatory substances, and cytokines directly or indirectly. Indeed, increased brain IL-1beta and TNF-alpha occur after viral or bacterial infection; these changes are likely responsible for the sleep responses associated with PRR stimulation. TLRs also activate the inflammasome leading to the activation of IL-1beta and TNF-alpha (see below) (75).

As already mentioned bacterial cell wall products such as muramyl peptides or LPS are PAMPs, and they are recognized by PRRs such as TLR2 or TLR4 (74). In the case of influenza virus, double-stranded (ds) viral RNA is the PAMP. The TLR3 recognizes viral ds RNA. Mice lacking TLR3 infected with mouse adapted influenza virus have reduced NREM sleep, body weight, and hypothermic responses compared to mice that possess that gene (76). Thus, PRRs are vital to the pathogen-induced sleep response by modulating inflammatory sleep regulatory substances.

8. SLEEP IS A LOCAL INFLAMMATORY PHENOMENON

Sleep always occurs following experimental- or pathological-induced brain lesions (1). This suggests that no specific area of brain is necessary for sleep to occur and that sleep is a fundamental self-organizing process of neuronal/glial networks. Regardless, the sleep disturbances following lesions are likely due to the local destruction of neurons and glia and subsequent inflammation and dysregulation of a competent inflammatory response necessary for normal sleep.

Sleep is a neuronal/glial network use-dependent process (1, 77). Increased slow wave sleep occurs following cognitive tasks or afferent stimulation in humans and/or rodents. Further, prolonged wakefulness associated with higher levels of neuronal activity and subsequent slow wave sleep responses. Moreover, the stimulation of specific whiskers of rodents' increases cytokine expression and the probability of a sleep-like state occurring in the corresponding cortical column that receives afferent input from the stimulated whisker (78).

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Intriguingly, sleep is not only use-dependent but also occurs locally (1, 77). This is evident in animals including birds and marine mammals that have unilateral sleep. Further, the aforementioned whisker stimulation and reciprocating sleep are localized to the stimulated column(s) (78). Further, in rodents, the administration of TNF- α directly onto a cortical column induces a sleep-like state in that particular column (79). In addition, the application of TNF- α or IL-1 β onto the cortex unilaterally enhances the intensity of NREM sleep ipsilaterally, but not contralaterally, without altering REM sleep or wakefulness (80, 81). Collectively, these findings suggest that sleep occurs locally and is mediated by local inflammatory sleep regulatory substances. In fact, this observation is logical since sleep regulatory substances such as cytokines mostly act locally through paracrine and autocrine mechanisms. While sleep regulatory circuits are not the impetus for sleep, they likely mediate the coordination of local sleep for the emergence of whole animal sleep. However, the exact mechanisms governing the coordination of local sleep into whole animal sleep remains unclear.

9. EXTRACELLULAR ATP

Local sleep and inflammatory processes are mediated, in part, by extracellular ATP. ATP is found in glia and neuronal synaptic vesicles, with 10-50 times higher presence in the vesicles than in the cytosol (82). ATP is co-released into the extracellular space with neurotransmitters including glutamate and GABA.

Extracellular ATP is broken down to adenosine through enzymes within the brain (83). Ectonucleoside triphosphate diphosphohydrolase (i.e. CD39) converts ATP and adenosine diphosphate to 5'adenosine monophosphate (AMP). AMP is then converted to adenosine by the 70-kDa glycosylphosphatidylinositol anchored ectoenzyme, ecto-5'-nucleotidase (i.e. CD73). CD39 and CD73 are found in many types of CNS cells, including glia and neurons. Interestingly, extracellular adenosine acting via the purine type 1 receptor, adenosine A2A, is regarded as an anti-inflammatory molecule which may alter sleep-related inflammation (84). We recently found that mice lacking CD73 have increased spontaneous sleep (Zielinski *et al.*, unpublished observations). Although the mechanisms governing this observation have not been determined, our finding implicates the somnogenic actions of ATP and the modulation of inflammation by CD73 enzymatic activity.

The energy depletion hypothesis of sleep suggests that neuronal activity depletes mitochondrial ATP to enhance sleep (85). However, oxidative phosphorylation increases following sleep deprivation suggesting that wakefulness increases neuronal/glia ATP production and extracellular ATP release rather than reducing it (86). Moreover, the most robust depletion of mitochondrial ATP via exercise has very modest effects on altering sleep (87). Consequently, an extracellular ATP hypothesis is more plausible (1). Extracellular ATP increases following sleep deprivation and local use, and it is recognized by purine type 2 receptors, including the P2X7 receptor (88).

Purinergic receptors are found widely in glia. Extracellular ATP via purinergic receptor recognition on microglia affect many sleep regulatory substances including IL-1 β , TNF- α , BDNF, cyclicAMP, phospholipase C, arachidonic acid, and NO (15, 89). Indeed, we recently found that ATP agonists enhance affects sleep while ATP antagonists inhibit sleep, in part, through the P2X7 receptor.

An important mediator between extracellular ATP or pathogenic induction of cytokine activation and sleep is likely the inflammasome. Inflammasomes are present in brain cells including glia and neurons (75). Extracellular ATP, LPS, and bacteria induce activation of the inflammasome and subsequent cytokine production. Caspase-1 activity is regulated by the nacht domain-, leucine-rich repeat, and pyrid domains-containing protein 3 (NALP3) inflammasome. IL-1 β and IL-18 are regulated by caspase-1, which cleaves their pro-forms (i.e. pro-IL-1 β and pro-IL-18) into their active forms. Indeed, evidence indicates that caspase-1 activation modulates sleep. For example, inhibiting caspase-1 reduces LPS-induced inflammation and enhanced sleep (90).

Extracellular ATP activation of purine receptors induces the release of intracellular potassium, an event that is dependent upon cell membrane pore formation (75). ATP-induced loss of intracellular potassium induces the activation of the NALP3 inflammasome. When potassium efflux is blocked by exogenous potassium, however, the ability of ATP to induce IL-1 β and IL-18 is also blocked. Membrane potassium trafficking is involved in sleep regulation. Knockout mice of Kv3.2 (a channel present in neurons and glia) have reduced EEG NREM delta power (91). The shaker and sleepless genes that regulate sleep duration are part of voltage-gated potassium ion channels (92, 93). Moreover, mice lacking Kcna2 (which codes for Kv1.2 the alpha subunit of shaker potassium channel) have less spontaneous NREM sleep than wild types, although these mice do not respond differently to 6 h of sleep deprivation (94). Thus, a plausible mechanism for the sleep regulatory actions of potassium is through the activation of the inflammasome.

10. CONCLUSION

Sleep modulates and is modulated by inflammation, and inflammation induced by pathogens alters sleep. The inflammatory process is complex and involves interactions between neurons and glia to regulate sleep. These actions are targeted to local areas. Many sleep regulatory substances and their respective receptors and cellular pathways mediate inflammation to alter sleep; thus, inflammation produced via local activity or pathogen recognition is the impetus for sleep.

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