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Sleep and Cytokines

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Introduction

Physiologic processes including sleep are regulated in part by humoral substances. Cytokines as pleiotropic signaling molecules are involved in the regulation of many such processes. The study of the humoral regulation of sleep began almost 100 years ago with the publication of Ishimori's[1] and Legendre and Pieron's[2] work showing that the transfer of cerebrospinal fluid from sleep-deprived dogs into normal dogs enhanced sleep in the recipients. These findings led to several searches dedicated to the identification of the responsible substances. These searches were conceptually based on the hypotheses that; (1) sleep is regulated, in part, by humoral agents within the nervous system, and (2) those agents undergo concentration or conformational changes that track, and thereby potentially provide an index of, cumulative sleep/wake history. Although many have replicated those original findings in similar experiments (eg, Ref.[3] and reviewed in Ref.[4]), this search continues. Many substances are implicated in sleep regulation. These sleep regulatory substances (SRSs) range from low-molecular-weight substances with short half-lives (eg, adenosine, nitric oxide [NO]), to longer-lived peptides, such as growth hormone-releasing hormone and orexin, and proteins including the cytokines. Until recently, the brain mechanisms that index sleep/wake history to SRS activity were unknown. Two cytokines, interleukin 1 β (IL-1) and tumor necrosis factor α (TNF), are well characterized for their roles in sleep regulation and are used to show these newer ideas in this review.

Many experimental approaches have been used to discover and characterize SRSs (reviewed in Refs.[4–6]). All of these approaches, including methods such as the use of transgenic animals, epigenetic and posttranslational modifications, and proteomic and genome-wide searches, are limited because sleep cannot be isolated as an independent variable. Virtually every physiologic parameter (eg, body temperature, hormonal levels, respiration rate, urinary output, brain metabolism, feeding and reproductive behaviors) changes with sleep. As a consequence, it is not possible to definitively know, for example, whether the change in

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expression of a particular molecule that correlates with sleep or sleep loss does so as a direct consequence of sleep or of some other concurrent physiologic process. Sleep researchers have developed lists of criteria that candidate SRSs need to meet before they can be reasonably proposed as being involved in sleep regulation (Box 1).[6–9] The usefulness of a multiple criteria approach to identify SRSs is that it limits false detection. Adherence to these criteria is especially important because many substances are capable of altering sleep (eg, alcohol). To date, only a few substances have met all of these criteria; IL-1 and TNF are among them.

Our knowledge of SRS involvement in processes believed to be unrelated to sleep has led to unexpected developments in our understanding of sleep mechanisms and how the brain organizes sleep. For example, our view of what exactly it is that sleeps has shifted from whole organisms to neural networks such as cortical columns (also called neuronal assemblies or neuronal groups). Our departure from the canonical view that sleep is a global process distributed across the brain was deduced from the fact that all SRSs identified play a role in activity-dependent neural plasticity. This finding suggests that 1 important function of sleep is to facilitate neural connectivity. The roles that cytokines play in these developments are discussed later.

TNF and IL-1 Meet all the Criteria for SRSs

Systemic or central injection of either TNF or IL-1 enhances duration of NREMS and EEG δ wave power during NREMS in every species thus far tested including, mice, rats, rabbits, cats, sheep, monkeys, and humans (criterion 1; see Box 1) (reviewed in Refs.[4,10,11]). After intracerebroventricular (ICV) or intraperitoneal (IP) injections of either IL-1 or TNF, increases in NREMS manifest within the first hour and, depending on dose, last up to 8 to 12 hours. The effects on NREMS can be large (eg, after 3 μg of TNF IP, mice spent an extra 90 minutes of NREMS over the first 9 postinjection hours[12] and after 600 fmol ICV IL-1 rabbits spent an extra 2 hours in NREMS over the first 12 post-injection hours).[10] The effects on rapid eye movement sleep (REMS) are dependent on route of administration, time of day, and dose. For instance, low somnogenic doses usually do not alter duration of REMS, whereas high somnogenic doses inhibit REMS. High doses of either IL-1 or TNF inhibit sleep; the sleep responses after these high doses resemble the sleep that occurs during severe infectious disease (eg, sleep episode duration is shortened). Somnogenic doses of IL-1 or TNF also increase δ wave power during NREMS,[12,13] a measure of sleep intensity.

The brain is susceptible to sleep disruptions, often over periods of days or more. Prolonged bouts of wakefulness are followed by sleep rebound, sometimes over multiple subsequent sleep periods. Sleep rebound is characterized by increased time spent in sleep and increased sleep intensity as defined by larger amplitude of EEG δ waves. Sleep homeostasis is a defining characteristic of sleep and its mechanisms likely involve the production and release of SRSs, including IL-1 and TNF. Thus, injection of exogenous IL-1 or TNF induces an NREMS that resembles sleep after sleep loss in that its duration and intensity are greater. Further, if either IL-1 or TNF is inhibited during sleep loss, the expected subsequent sleep rebound is greatly attenuated (reviewed in Ref.[14]). These latter findings coupled with the

evidence presented in the previous paragraph strongly implicate IL-1 and TNF in sleep homeostasis.

Inhibition of either IL-1 or TNF using several different approaches reduces spontaneous NREMS (criterion 2; see Box 1). For example, the IL-1 receptor antagonist (an endogenous gene product), IL-1 and TNF soluble receptors (also endogenous substances), and anti-IL-1 or anti-TNF antibodies inhibit NREMS if given to experimental animals [reviewed in Ref.[4]). In humans, the TNF soluble receptor is a normal constituent of cerebrospinal fluid and inhibits sleep[15] and fatigue.[16] Substances that inhibit the production, release, or actions of IL-1 or TNF also inhibit duration of NREMS. For example, glucocorticoids, IL-4, IL-10, and IL-13, and corticotrophin-releasing hormone all inhibit IL-1 and TNF and reduce spontaneous NREMS (reviewed in Ref.[4]).

Another approach to inhibit SRSs is to remove 1 or more of the genes in its signaling pathway. Knockout mice that lack either the IL-1 type I receptor (IL1R1),[13] the brain-specific IL1R1 accessory protein,[17] the TNF 55-kD receptor[12] or both IL1R1 and TNF receptor (TNFR)[18] have less spontaneous sleep than control strains of mice. The NREMS deficits in the TNF 55-kD receptor knockout mice occur mostly during the first hours of daylight, whereas the NREMS deficits in the IL1R1 and double TNF/IL-1 receptor knockout mice occur mostly during the nighttime. The results from those studies suggest some independence of the somnogenic actions of IL-1 and TNF, although these cytokines induce each other in brain in vivo.[13] Further, the TNF receptor knockout mice show NREMS responses if given IL-1[13] and the IL-1 receptor knockout mice do likewise if given TNF.[12]

Brain levels of either IL-1 or TNF or their respective mRNAs vary with sleep propensity (criterion 3; see Box 1). For example, IL-1 cerebrospinal fluid levels in cats vary with the sleep/wake cycle.[19] Spontaneous brain levels of IL-1 mRNA and TNF mRNA vary with sleep propensity in rats, with highest levels occurring at the onset of daylight hours (reviewed in Ref.[4]). Rat hypothalamic (an NREMS regulatory network) levels of both IL-1[20] and TNF[21] are highest at the time when spontaneous NREMS duration is greatest. Cerebral cortical levels of IL-1 and TNF also vary with the time of day. If sleep propensity is enhanced by sleep deprivation, both IL-1 mRNA and TNF mRNA levels increase in brain (reviewed in Ref.[4]). Further, if rats are fed a cafeteria diet their NREMS is enhanced, as are their hypothalamic IL-1 mRNA levels.[22] During infectious disease states when sleep in enhanced, brain levels of IL-1 and TNF mRNAs are enhanced (eg, during influenza virus infections in mice).[23]

If either IL-1 or TNF is microinjected into sleep regulatory circuits, NREMS is enhanced (criterion 4; see Box 1). Thus, microinjection of TNF into the anterior hypothalamus is associated with dose-dependent increases in NREMS.[24] In contrast, injection of the TNF soluble receptor into the anterior hypothalamus inhibits spontaneous NREMS. Similarly, an extensive study of IL-1-responsive sites indicated that sites near the ventricles and subarachnoid sites near the hypothalamus are associated with enhanced NREMS.[25] Further, IL-1 receptive hypothalamic neurons also are receptive to growth hormone-releasing hormone, another well-characterized SRS (reviewed in Ref.[4]), and those neurons are γ-aminobutyric acid-releasing (GABA)-ergic.[26] If growth-hormone-releasing hormone

(GHRH) is microinjected into the hypothalamus, it induces sleep responses and activity in sleep-active neurons.[27,28] Sleep-active hypothalamic neuron firing rates are enhanced by IL-1, whereas wake-active hypothalamic neurons are inhibited.[29] Classic brain stem sleep/wake circuits are also modulated by SRSs. For example, microinjection of either IL-1 or TNF into the locus coeruleus[30] or IL-1 into the dorsal raphe[31] enhances NREMS. IL-1 suppresses wake-active serotonergic neurons in the dorsal raphe[32] by affecting GABA[33] and possibly its receptor availability.[34] Collectively, these data indicate that IL-1 and TNF act on sleep regulatory circuits to enhance NREMS. Both cytokines also have the capacity to act directly on the cerebral cortex to enhance sleep intensity regionally, and that suggests that these substances can act throughout the neuraxis to alter state within neuronal assemblies. This view of brain organization of sleep is discussed later.

Many diseases with associated changes in sleep propensity also alter cytokines (criterion 5; see Box 1). The changes in hypothalamic cytokines associated with influenza virus in mice have already been mentioned. Human studies have greatly enriched the literature relating circulating cytokines to disease-associated sleepiness. TNF plasma levels are increased in multiple diseases associated with enhanced sleepiness, including patients with AIDS, chronic fatigue, insomnia, myocardial infarct, excessive daytime sleepiness, postdialysis fatigue, preeclampsia, alcoholism, obesity, sleep apnea (reviewed in Ref.[4]), and Alzheimer disease.[35] The TNF polymorphic variant, G-308A, is linked to metabolic syndrome[36] insulin resistance,[37] sleep apnea,[38] and heart disease.[39] Systemic endotoxin, a gram-negative bacterial cell wall product, enhances sleep and plasma TNF levels in humans.[40] Clinically approved inhibitors of TNF (eg, etanercept) reverse the sleepiness and fatigue associated with sleep apnea,[15] rheumatoid arthritis,[16] ankylosing spondylitis,[41] and alcoholism.[42] Surgical treatment of, or CPAP treatment of, obstructive sleep apnea reduces TNF/TNFR plasma levels.[43–45]

Blood levels of IL-1 in humans may also vary with sleep propensity, but this literature is not as clear as that for TNF. IL-1 plasma levels peak at the onset of sleep[46] and are enhanced during sleep deprivation.[47,48] Circulating levels of either TNF or IL-1 affect sleep via the vagus nerve because vagotomy blocks IP TNF-enhanced[49] or IL-1-enhanced[50] NREMS. Systemic injections of either IL-1 or TNF enhance brain levels of IL-1 and TNF mRNAs.[51] Vagotomy also blocks the IP IL-1-enhanced hypothalamic IL-1 mRNA.[52] Collectively, it seems that the sleep disturbances associated with disease are mediated in part via IL-1 and TNF (reviewed in Ref.[53]). Given the strong relationship of IL-1 and TNF with sleep in both health and disease states, their importance in sleep medicine will continue to grow.

Associated Mechanisms of IL-1-Enhanced and TNF-Enhanced Sleep

The regulation of the brain cytokine network is not fully understood. Regardless, a variety of cytokines and cytokine-associated substances have been shown to alter sleep. Several of these such as the IL-1 and TNF soluble receptors have already been mentioned. Cytokine-associated substances such as the IL-1 receptor antagonist and several antisomnogenic substances, such as IL4, IL-10, IL-13, and transforming growth factor b, inhibit spontaneous NREMS. In contrast, other cytokines such as IL-6, IL-18, acidic fibroblast growth factor, interferon γ, nerve growth factor, brain-derived neurotrophic factor, and glia-derived

neurotrophic factor, promote NREMS (reviewed in Ref.[4]). There are some cytokines that apparently do not affect sleep, at least under the conditions tested; these include interferon β[54] and basic fibroblast growth factor.[55] Nevertheless, IL-1 and TNF affect many other molecules that in turn affect sleep. Nuclear factor κ B (NFκB) and c-Fos (AP-1) are transcription factors that are activated by IL-1 and TNF (reviewed in Refs.[4,53]). These transcription factors promote production of IL-1 and TNF and many other substances implicated in sleep regulation including multiple cytokines, the purine type 1 receptor adenosine A1 receptor (A1AR), cyclooxygenase 2, and GHRH receptor. NFκB is activated within the hypothalamus and cortex by sleep deprivation.[56,57] Adenosine also elicits NFκB nuclear translocation in basal forebrain slices via the A1AR.[58] An inhibitor of NFκB inhibits NREMS.[59] IL-1 and TNF also affect many small molecules with short half-lives that are involved in sleep regulation. including NO, adenosine and prostaglandins (reviewed in Ref.,[4] eg, Ref.[60]). For example, inhibition of NO synthase blocks IL-1-induced increased NREMS responses.[61] Cytokines also interact with multiple neurotransmitters involved in sleep regulation including GABA, norepinephrine, serotonin, and acetylcholine (reviewed in Ref.[4]). The cytokine network is characterized by redundancy, positive feedback loops, extensive cross-talk, autoregulation, and many other complexities; most of it remains to be studied within the context of sleep. The exact somnogenic biochemical pathways affected by cytokines likely depend on circumstances such as time of day, waking activity, and disease, although it seems clear that known SRSs work in concert with each other to affect sleep.

Brain Organization of Sleep: Cytokine Involvement in Cortical Column State

Sleep researchers have yet to reach consensus as to exactly what it is that sleeps. This problem has the potential to confuse discussions of sleep regulation. For instance, traditionally sleep was considered a whole-animal phenomenon: either the subject was asleep or awake. However, it is now clear that some marine mammals show unihemispheric sleep (reviewed in Ref.[62]). Further, some characteristics of sleep such as EEG δ wave activity, metabolism, and blood flow manifest regionally depending on previous waking activity in those regions. In addition, a fundamental meta-finding within sleep research is that regardless of where a lesion in the brain may occur, if the subjects survive, they sleep. This finding strongly indicates that sleep is an intrinsic property of any viable neuronal network and, contrary to the prevailing sleep regulatory paradigm, that sleep regulatory circuits do not impose sleep on the brain, because if they are lesioned, the animal sleeps (reviewed in Ref.[63]).

These considerations led us and others to propose that sleep is a fundamental property of neural networks.[64–67] It is possible that individual cells may sleep, but if one entertains this hypothesis, definitional problems are confronted (eg, is a silent neuron, or a bursting neuron, asleep? Most likely not, because such firing patterns can be found in conditions not associated with sleep). There also seems to be little chance of causally connecting activity of a single neuron to a state beyond correlation of firing rates. The positing of a brain organization level at which sleep emerges allows falsifiable hypotheses to be made at the appropriate level of organization. By way of analogy, to study the heat capacity, osmotic properties, vapor pressure, or taste of water, one does not study H or O; these emergent properties are the result of combining H and O and are fundamentally not predictable from

our current knowledge of H or O. To relate our hypothesis to our past work with cytokines, we framed it within a biochemical mechanistic causal proposal (Box 2). There is now considerable evidence for the hypothesis and it is discussed in this section.

There is cell activity-dependent expression of cytokines in brain (step 1; see Box 2). This is well known for cytokines such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (reviewed in Ref.[68]), but is less studied for IL-1 and TNF. Conditions such as kindling, sleep deprivation, or extracellular glutamate enhance brain IL-1 or TNF, suggesting that excessive activity or excitatory stimuli are responsible.[69–72] Data from our laboratory indicate that within cerebral cortical neurons or glia, TNF and IL-1 are enhanced if afferent neuronal activity into the specific column is enhanced.[73,74] Collectively, such data strongly suggest that cytokine expression in neurons/glia is activity dependent.

The activity-dependent cytokines act on neurons to change their electrical and responsive properties (step 2; see Box 2). For some cytokines such as NGF and BDNF, this process is well established. For IL-1 and TNF, it has also been studied, but within the context of the fever literature (reviewed in Ref.[75]). For instance, IL-1 or TNF alter hypothalamic neuron sensitivity to temperature. TNF upregulates, whereas IL-1 downregulates glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression in neurons (see later discussion), and changed populations of AMPA receptors alter neuronal response patterns. IL-1 receptors on hypothalamic neurons colocalize with GHRH receptors on GABAergic cells.[26] IL-1 enhances presynaptic release of GABA in hypothalamic cells.[76] IL-1 enhances hypothalamic sleep-active neurons and inhibits wake-active neurons.[29] There is thus ample evidence indicating that cytokines act on neurons to change their electrical properties.

These cytokine-induced altered neuronal properties affect sleep phenotype. Thus if either IL-1[77] or TNF[78] is applied to the surface of the cortex unilaterally, there is a dose-dependent and state-dependent increase in EEG δ power on the side receiving the cytokine. The increases occur during NREMS but not during REMS or waking and are confined to the 0.5-Hz to 4-Hz frequency band. Further, if TNF expression is unilaterally inhibited using a small-interfering RNA (siRNA) within the cortex, there is a reduction of EEG δ power unilaterally.[79] If rats are deprived of sleep and pre-treated with a TNF soluble receptor or an IL-1 soluble receptor, the enhanced EEG δ wave power that occurs during subsequent NREMS is attenuated.[77,78] Together, these data suggest that TNF and IL-1 are produced in response to activity and act locally on networks to change input-output properties, resulting in a regionally more intense sleep or if inhibited a regionally less intense NREMS.

There is direct evidence that neuronal assemblies oscillate between 2 or more functional states and one of these states is induced by TNF and is sleeplike in character (step 3; see Box 2). If cortical columns are probed with afferent stimulation and subsequent amplitudes of evoked potentials are measured, different functional states can be determined.[80] One of those states correlates with whole-animal sleep and the probability of entering that state is dependent on previous afferent input to the column and past state status. Excessive afferent input to a cortical column increases the likelihood that the column enters the sleeplike state. Similarly, the longer the column is in a wakelike state, the higher the probability that later it

enters the sleeplike state. These properties of cortical column sleeplike states are also properties of whole-animal sleep. Further, cortical column state affects behavior. If rats are trained to lick in response to stimulation of a whisker, the error rate is higher if the cortical column of the stimulated whisker is in the sleeplike state than if it is in the wakelike state.[81,82] Localized injection of TNF onto cortical columns induces the sleeplike state in the affected columns.[78] These data suggest that sleep is a fundamental property of neuronal assemblies.

During organism sleep and wake, most of the columns are in their respective sleeplike and wakelike states, suggesting synchrony of state between columns (step 4; see Box 2). Columns are topographically organized, and in general, the closer a column is to another, the more tightly the 2 are linked by neural and humoral connections. Because they are linked, it is likely from a theoretic view that they functionally synchronize with each other.[83,84]

Cortical columns are also connected to subcortical sleep regulatory circuits (step 5; see Box 2). Unilateral injection of either TNF or IL-1 onto the cerebral cortex activates reticular thalamic neurons as determined by fos expression.[85,86] Further, prefrontal cortical neurons, ventral lateral preoptic neurons, and medial preoptic neurons are also activated by IL-1.[86] These data suggest that the status of cortical column state could be relayed to these NREMS regulatory networks. It is also possible that these regulatory networks are thus involved in coordinating whole-animal sleep using cortical column state status information. Thus in this view sleep is (1) dependent on previous cellular activity, (2) initiated at the cortical column level, (3) a self-organized state being coordinated between columns and being a statistical property of the number of columns is the sleeplike state, and (4) it is refined and timed into whole-animal sleep by sleep regulatory networks. Each of these is a falsifiable hypothesis.

A Neuroconnectivity Function for Sleep: Cytokine Involvement

Sleep as a subject of neurobiology is unusual because its function has not been experimentally defined. Its importance is shown by the facts that during sleep one does not reproduce, eat, drink, or socialize and one is subject to predation. These are high evolutionary costs to overcome by whatever the beneficial effects of sleep are. So what could be so important to the brain to allow such a disadvantaged state to persist? There are many theories of sleep function positing that the answer is neural connectivity.[66,87–91] In this review, we focus on just 2 (our own[89] and that of Kavanau[66]) because the logic of the 2 is similar and both are derived in part from the earlier proposal of Roffwarg.[92] The central idea of both theories was the recognition that use-dependent changes in synaptic efficacy and connectivity would lead to dysfunction unless there were processes to stabilize synaptic networks that are constantly being modified by activity. This process is now termed synaptic scaling. Synaptic scaling serves to regulate Hebbian plasticity; thus, an increase in network activity causes a slow compensatory decrease in excitatory synaptic efficacy, whereas a decrease in network activity enhances excitatory synaptic strength.[93] The stabilization mechanism proposed by us was SRS-induced changes in local electrical properties, whereas the mechanism proposed by Kavanau was intrinsic spontaneous electrical activity. These mechanisms are not mutually exclusive and both are scaling mechanisms. More recent sleep-connectivity theories have also invoked synaptic scaling (reviewed in Refs.[94,95]).

Of importance to this review is that TNF is involved in synaptic scaling. Thus, TNF promotes AMPAreceptor expression and enhances cytosolic Ca^{++} levels.[96] This TNF action is physiologic because an inhibitor of TNF inhibits AMPA-induced postsynaptic potentials[97] and AMPA-induced changes in cytosolic Ca^{++}.[96] A TNF siRNA applied to the cortex inhibits gluR1 mRNA levels[79]; gluR1 is a subunit of the AMPA receptor. AMPA receptors are involved in EEG synchronization[98] and synaptic plasticity.[99] Direct evidence for the involvement of TNF in synaptic scaling has been described.[100] IL-1 may also affect AMPA receptor expression.[101] AMPA receptors in layer V are involved in downscaling during NREMS.[102] Overall, these data suggest a cytokine-dependent mechanism for the reconfiguration of synaptic weights during NREMS.

Connecting Activity to Cytokines: The Adenosine Triphosphate-Cytokine-Adenosine Hypothesis

A major tenant of the neuroconnectivity theories is their dependence on activity. Indeed, within the brain, a major stimulus for IL-1 and TNF production and release is neuronal activity. Adenosine triphosphate (ATP) is coreleased with neurotransmitters.[103] ATP in turn induces IL-1[104] and TNF[105] release from glia via P2X receptors (reviewed in Refs.[106,107]). ATP is present in neuronal synaptic vesicles. The concentration of ATP in the vesicles is 10 to 50 times higher than in the cytosol. In the brain, ATP is coreleased in GABAergic, cholinergic, noradrenergic, and glutamatergic synapses. ATP is also considered a gliotransmitter. Once released, some extracellular ATP is converted to adenosine. In turn, adenosine binds to the other major purine receptor types, P1 receptors (Fig. 1). The action of adenosine is fast, occurring within milliseconds to seconds, and it results in increased K+ permeability and hyperpolarization.

Some of the released extracellular ATP acts on glial P2Rs and causes the release of IL-1, TNF, and BDNF as well as additional ATP (see Fig. 1). IL-1 precursor is processed by caspase 1, which is triggered via ATP activation of P2X7 receptors.[108,109] TNF and IL-1 released from glia act more slowly (minutes to hours) on adjacent neurons, leading to the activation of NFκB. NFκB promotes transcription of receptor mRNAs such as the adenosine A1R and the glutamate AMPA receptor-gluR1 mRNAs. Translation of those mRNAs into their respective proteins and their subsequent expression on the cell membrane would change sensitivity of the postsynaptic neuron over longer periods. This is a prototypical scaling effect, because the expression of postsynaptic receptors is modulated by the activity of the presynaptic neuron (ie, the amount of released ATP). Thus, the sensitivity of the postsynaptic neuron is scaled to the previous use of the synapse. As mentioned, TNF and BDNF are the 2 molecules most firmly linked to synaptic scaling. Thus, ATP levels are affected by metabolism and neural activity and in turn affect extracellular levels of adenosine and cytokines, thereby providing direct links between neural activity, metabolism, and sleep regulation. This idea fostered our ATP-adenosine-cytokine hypothesis.[89] Mechanistically, our hypothesis is summarized as follows: (1) neuronal activity is associated with gliotransmission and neurotransmission corelease of ATP; (2) the consequent increase in extracellular ATP thus provides an index of previous local neuronal activity; (3) the ATP is detected by nearby purine type 2 receptors, causing the release of sleep regulatory

cytokines such as TNF, IL-1, and BDNF, and this provides for the translation of previous neuronal activity into local levels of SRSs; (4a) these substances in turn, by a slow process (gene transcription/translation), alter electrical properties of nearby neurons by altering their own production and that of receptor populations, such as glutamate and adenosine receptors; (4b) the SRSs also, by a fast process (diffusion for short distances), directly interact with their receptors on neurons and alter electrical properties; (4c) further, ATP itself breaks down, releasing extracellular adenosine, which in turn acts on adenosine receptors, again altering electrical potentials on the nearby neurons. These events are happening locally and the collective electrical changes result in a shift in input-output relationships within the local neuronal assemblies that originally showed the increase in activity (ie, a state shift). In a mathematical model, the local states of neuronal assemblies rapidly synchronize, or phase lock, with each other because they are loosely connected to each other via neurons and humoral substances.[84] Well-characterized sleep regulatory circuits and associated activation networks play a critical role in both sleep and waking by ensuring the synchronization of neuronal assembly state for niche-adaptation purposes. Consistent with this model, ATP agonists promote NREMS, whereas ATP antagonists inhibit sleep.[110] Further, after sleep deprivation, mice lacking the P2X7 receptor have attenuated duration of NREMS and EEG d wave power during NREMS compared with control mice.[110]

Summary

IL-1 and TNF are well-characterized SRSs that form part of the sleep homeostat (see Fig. 1). Our knowledge of cytokine sleep mechanisms has led to a view of brain organization of sleep positing that sleep is a local property of neural networks being initiated, for example, within cortical columns. Cortical columns oscillate between functional states; the sleeplike state of cortical columns is promoted by TNF. Further, TNF is involved in glutamatergic AMPA receptor expression and in synaptic scaling mechanisms. Cytokine-mediated sleep mechanisms provide support for the hypothesis that sleep serves a synaptic-connectivity function and is tightly coupled to cerebral metabolism. IL-1 and TNF release from glia is enhanced by neuronal activity via ATP and, in turn, IL-1 and TNF activate NFkB, adenosine, and other downstream mechanisms.

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Key Points

- Interleukin 1 (IL-1) and tumor necrosis factor (TNF) are well-characterized sleep regulatory substances that form part of the sleep homeostat.
- A large literature showing of cytokine involvement in the brain organization of sleep corroborates the view that sleep is an emergent property of neural networks such as cortical columns.
- Cortical columns oscillate between functional states; the sleeplike state of cortical columns is promoted by cytokines. Further, cytokines are involved in synaptic scaling mechanisms and are therefore capable of modulating network activity.
- The function(s) of sleep is still debated; however cytokine-mediated sleep mechanisms support the hypothesis that sleep serves a synaptic-connectivity function.
- How the brain tracks activity and mediates sleep homeostasis is posited in our ATP-cytokine-adenosine hypothesis, wherein IL-1 and TNF release from glia is enhanced by neuronal activity via adenosine triphosphate and, in turn, IL-1 and TNF activate nuclear factor κ B, adenosine, and other downstream effectors to locally influence state.

Box 1 Criteria for SRSs

1. The SRS should enhance a sleep phenotype (eg, duration of non–rapid eye movement sleep (NREMS) or electroencephalographic (EEG) δ wave power).
2. Inhibition of the SRS should reduce spontaneous sleep.
3. The SRS levels in the brain should correlate with sleep propensity.
4. The SRS should act on putative sleep regulatory circuits
5. The SRS levels in disease should correlate with sleepiness.

Derived from Refs.[6–9]

Box 2 Sleep mechanisms

1. There is activity-dependent production of SRSs.
2. Activity-dependent SRSs act locally on nearby neurons/glia to change their electrical/receptive properties and thereby alter the input-output relationships of the networks within which they are found.
3. Altered input-output relationships within neuronal assemblies indicate functional state changes of the assemblies.
4. Synchrony of state between semiautonomous neural assemblies occurs because they are loosely connected via neurons and humoral substances.
5. Sleep regulatory circuits coordinate neuronal assembly functional state changes into organism sleep.

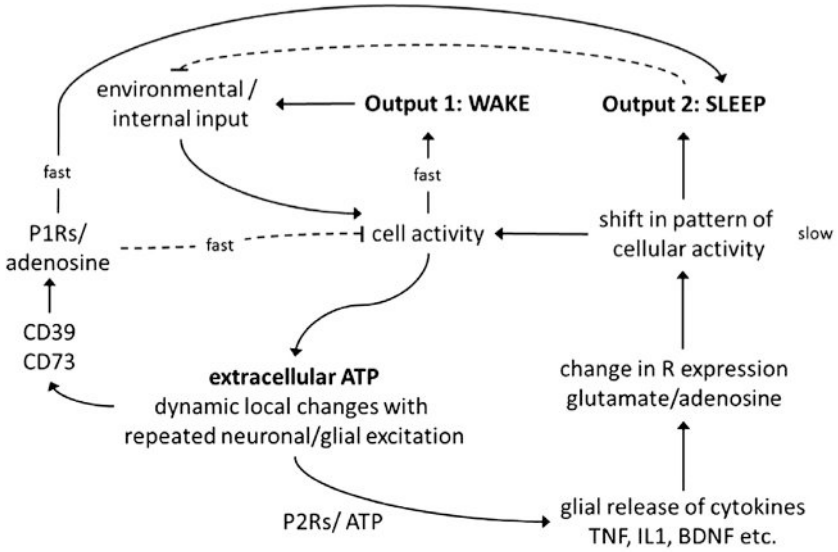

Fig. 1.

The sleep homeostat. Molecular networks operating on different timescales (fast vs slow) comprise the sleep homeostat. Cellular activity is induced and sustained by environmental stimuli. Cellular activity increases arousal (*output 1*) and causes ATP to be coreleased with glutamate and other neurotransmitters. This extracellular ATP provides a way for the brain to track previous activity; some ATP is enzymatically converted to adenosine (fast) and some binds with glial P2 receptors to facilitate SRS secretion. SRSs induce fast-acting labile substances like adenosine and NO. Alternatively, SRSs and their effectors can lead to alterations (slow) in receptor content and receptor-mediated ion gating, causing a shift in overall cellular activity. Resulting changes in receptor populations predispose affected networks (within the diffusible range of extracellular ATP) to sleep (*output 2*).