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THEORETICAL REVIEW

Local sleep

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SUMMARY

The historic sleep regulatory paradigm invokes "top-down" imposition of sleep on the brain by sleep regulatory circuits. While remaining conceptually useful, many sleep phenomena are difficult to explain using that paradigm, including, unilateral sleep, sleep-walking, and poor performance after sleep deprivation. Further, all animals sleep after non-lethal brain lesions, regardless of whether the lesion includes sleep regulatory circuits, suggesting that sleep is a fundamental property of small viable neuronal/glial networks. That small areas of the brain can exhibit non-rapid eye movement sleep-like states is summarized. Further, sleep-like states in neuronal/glial cultures are described. The local sleep states, whether *in vivo* or *in vitro*, share electrophysiological properties and molecular regulatory components with whole animal sleep and exhibit sleep homeostasis. The molecular regulatory components of sleep are also involved in plasticity and inflammation. Like sleep, these processes, are initiated by local cell-activity dependent events, yet have at higher levels of tissue organization whole body functions. While there are large literatures dealing with local initiation and regulation of plasticity and inflammation, the literature surrounding local sleep is in its infancy and clinical applications of the local sleep concept are absent. Regardless, the local use-dependent sleep paradigm can advise and advance future research and clinical applications.

Historical perspective

Sleep is often viewed as an animal behavior, yet the entire body is not required for sleep to ensue. Similarly, sleep is often viewed as "of the brain, by the brain, and for the brain" [1], yet the entire brain is not required for sleep. Further, sleep, metabolism, inflammation, and plasticity share numerous regulatory molecular components. All these processes, including sleep, are initiated locally yet have emergent whole-body manifestations and functions. This dialectic begs the questions: What is the minimal amount of brain tissue required for sleep? What exactly in brain sleeps? What are the causative signals initiating sleep in local networks? Answers to these questions will aid experimental approaches to sleep regulation and function. We argue herein that sleep is a fundamental process of small neuronal/glial networks initiated by cell activity-dependent molecular signals.

The concept of non-rapid eye movement sleep (NREMS) as a local, use-dependent, brain process is now tentatively accepted within the sleep research community [2,3]. Anomalies of the prior sleep research paradigm, that sleep is a whole brain phenomenon, began with Kristiansen and Courtois [4]. They showed that cortical slow waves, a key measure used to define NREMS, wax and wane within cortical islands lacking thalamic input but retaining their blood flow [4]. Slow electrical stimulation of many areas of brain induces a transient synchronized electroencephalogram (EEG) [5]. Although these findings suggest that the "entire encephalon has hypnogenic properties", Jouvet rejected this conclusion. Regardless, Jouvet showed that transection of the brain between the mesencephalon and diencephalon led to what could be defined as oscillations between NREMS and waking (W) anterior to the transection, while posterior to the transection a REMS-like state occurred [6]. Thus, different states can occur simultaneously within one brain. There is much clinical evidence concerning disassociated states, e.g., sleep walking, that reinforce the conclusions that different brain states can manifest simultaneously [7]. By extension, these findings point to local state regulatory events.

Although functional similarity likely exists between REMS and NREMS [2], differential biochemical and neuronal connectivity mechanisms within the varying levels of the central nervous system likely differentiate the two states. This was substantiated when transection between the mesencephalon and diencephalon

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Abbreviations

AcP	IL1 receptor accessory protein
AcPb	neuron-specific AcP
ATP	adenosine triphosphate
CD	cluster density
EEG	electroencephalogram
ERP	evoked response potential
fMRI	functional magnetic resonance imaging
GABA	gamma amino butyric acid
glu	glutamic acid
IL1	interleukin-1 beta
MEA	multi-electrode array
NREMS/REMS	non-rapid eye movement sleep/rapid eye movement sleep
PET	positron emission topography
TMS	transcranial magnetic stimulation
TNF	tumor necrosis factor alpha
W	waking

Glossary of terms

Evoked responsepotential	the brain's extracellular localized electrical response to an afferent input. ERPs can also be obtained from co-cultures of cells grown *in vitro* in response to a stimulus.
Local Sleep Definition	Local sleep is a complex physiological phenomenon occurring either within anatomically discrete brain locations *in vivo* or in cultured neuronal networks. As with global sleep, local sleep is defined through a combination of electrophysiological, homeostatic, molecular, genetic, and behavioral measures, including: delta power, synchronization, action potential burstiness, excess sleep-like response to prolonged wake-like states or activation and response to administration of somnogenic or wake-regulatory substances or stimuli.
OFF period	the period when cerebral cortical cells are hyperpolarized and have few action potentials. During NREMS, OFF periods oscillate with periods of action potential bursts at frequencies of about 1 Hz. OFF periods and bursting periods each last about 500 m s and they give rise to the 1 Hz component of EEG slow wave activity during NREMS.
Soluble receptor	The extracellular domain of many cytokine receptors can be cleaved and released into the extracellular fluid. Those domains retain the ability to bind their respective ligands and act to regulate extracellular cytokine concentrations.
Synaptic scaling	It is a homeostatic process whereby an increase in network activity induces a slow compensatory decrease in the efficacy of excitatory synapses. Conversely, a decrease in network activity increases in excitatory synaptic strength. Synaptic glutamic acid receptors are one set of receptors involved in synaptic scaling. Their activity-dependent changes within synapses, called trafficking, are regulated in part by some sleep regulatory substances, e.g., tumor necrosis factor alpha.

resulted in continuation of REMS-like states below the transection, and NREMS occurring in the isolated forebrain [6]. Accordingly, it seems reasonable to hypothesize that at a local network level, function of REMS in the brainstem is similar to that of NREMS in the forebrain and likely relates to brain plasticity [2]. Thus, local REMS may exist within the brainstem, but it is insufficiently studied primarily due to difficult experimental approach. However, cortical local sleep, including individual cortical column sleep, is likely a building block for NREMS.

Mukhametov described unilateral NREMS in dolphins [8,9]. These marine mammals lack NREMS simultaneously in both cerebral hemispheres and they do not have REMS. If one side of the brain is deprived of NREMS, that side, but not the contralateral side has subsequent sleep rebound [10]. Uni-hemispheric sleep occurs in other marine mammals and birds [11,12]. These studies demonstrate that part of the brain can be asleep while other parts are awake [13]. The land mammalian lesion and post-stroke literatures support this conclusion. Thus, regardless of the specific brain site intentionally lesioned, or damaged by cerebral infarcts if the animal or patient survives, they sleep, albeit not always normally. Remarkably, this is true even if the damage includes known sleep regulatory circuits. This information is derived from millions of post-stroke patients, as well as thousands of animal studies, and is one of the largest collective findings in sleep research. Although seldom mentioned, it indicates no specific area of brain is required for sleep to ensue. There are of course areas of brain required for life and one could argue that those areas also contain the so called "sleep center". That argument has been weakened by recent evidence showing: cortical column local sleep; local sleep homeostasis; targeted use-dependent intensity of sleep-linked measures such as EEG slow wave (0.5–4.0 Hz) power; use-dependent molecular mechanisms responsible for local and global sleep; and sleep-like states in tissue culture regulated by the same molecular mechanisms and expressing many characteristics used to define sleep, e.g., slow wave power, synchronization, burstiness, gene expression patterns and sleep homeostasis.

Local, use-dependent sleep

Krueger and Obal Jr. proposed that sleep served to stabilize the competitive use-dependent processes of synaptic formation and atrophy and thereby maintain the brain's plasticity while retaining adaptive network activity patterns sculpted from prior use [2]. Because plasticity is fundamentally a local use-dependent process, logically sleep followed suit. Inflammation is also a local process initiated in response to local tissue injury and microbes. We demonstrated that some of the molecular regulators of inflammation and plasticity, such as interleukin-1 beta (IL1) and tumor necrosis factor alpha (TNF), are expressed in normal brain and are involved in sleep regulation [3,14,15]. Much evidence over the past few years linked IL1 and TNF to synaptic mechanisms such as glutamate receptor trafficking and synaptic scaling [16–21]. Although the focus of our sleep function/mechanism theory was on the links to plasticity, we developed the inescapable conclusion

that sleep, like inflammation and plasticity, is initiated locally in response to cell activity, and involves many of the same molecules [2,3,15,22–24].

Many prior studies linked sleep function to plasticity [25]. These theories were derived from the learning and memory, computer, and physiological literatures and logic considerations [2,25–28]. These theories were built from the assumption that simple perceptions emerge from dynamic synaptic activation patterns. They also relied on the knowledge that synaptic activity, or lack thereof, strengthened, or weakened, synaptic efficacy. Thus, the brain is confronted with seemingly opposing synaptic challenges. New synapses, or enhanced synaptic efficacies, are needed to form and consolidate new synaptic activation patterns, thereby providing new memories. Sleep is involved in this process [29–31]. At the network level, recapitulation of waking network patterns occurs during sleep and is linked to memory formation [31,32]. There is a simultaneous need to preserve established adaptive synaptic networks so that prior memories can be maintained, accessed, and used, sometimes years later. Further, synaptic plasticity itself needs to be preserved because it has multiple selection advantages [2,26]. Finally, because the brain is always active, and synapses and synaptic efficacies are activity-dependent, synaptic pruning or synaptic down-scaling may be required as well [28,33]. Individual sleep function theories are proposed for each of these plasticity issues. Regardless, each requires a mechanism to label and select synapses for greater efficacy, preservation, or pruning; this is done at subcellular and cellular levels. One such mechanism is TNF-induced synaptic glutamate receptor trafficking involved in up- and down-synaptic scaling. Likely, multiple such molecular mechanisms within brain involving different synaptic mechanisms, neuromodulators, and transmitters exist, albeit each may scale their responses to activity stimuli differently. Regardless, these local molecular and subcellular mechanisms and network firing patterns occur within the context of feedback from emergent phenomena derived from higher level multi-cellular networks within which the synapses operate.

The sleep regulatory and function theories led to the hypothesis that sleep is initiated within any viable small neuronal/glial network. We now review evidential support for the local use-dependent sleep hypothesis [2].

Experimental evidence

Human studies

The first experimental test of the Krueger–Obal Jr. local use-dependent sleep hypothesis was reported by Kattler et al. [34]. They showed in humans that unilateral excessive activation of the somatosensory cortex, achieved by using a hand vibrating device, enhanced EEG slow wave power during subsequent sleep in the contralateral cortex (afferent somatosensory neurons cross over before reaching the cortex). In the Kattler et al. report, the increases were small, but significant [34]. During subsequent years their observation has been replicated many times using a variety of techniques including high density EEG recordings, various imaging methods, and recordings in animals [35]. Perhaps the related finding by Huber et al. is the most eloquent demonstration of the concept that activity during wakefulness affects local cortical depth of sleep [36]. After unilateral arm immobilization, subsequent EEG slow wave power was less in the contralateral cortex, thereby demonstrating that EEG slow wave power, and by inference sleep depth, can be manipulated up or down depending upon prior wake activity [36].

Other approaches to manipulate local brain activity combined with high density EEG indicate that local EEG delta wave activity, a defining NREMS criterion, is intensified during sleep in those areas activated in prior waking. De Gennaro and colleagues used paired associative stimulation, induced during wakefulness by peripheral nerve electrical stimulation coupled with a transcranial somatosensory cortex magnetic stimulation (TMS). This treatment induced localized higher delta wave amplitudes in subsequent sleep [37]. Similarly, high frequency repetitive TMS applied over the motor cortex led to an increase in localized EEG amplitude [38]. These data suggest that the magnitude of waking activity alters subsequent sleep intensity as measured by EEG delta wave activity.

Functional magnetic resonance (fMRI) and positron emission topography (PET) imaging have been used to similar ends. These methods measure relative changes in localized blood flow and metabolism. Local brain blood flow is “on-demand” regulated in that it is enhanced following local brain metabolism/activity [39]. A coarse orientation discrimination task during waking coupled with fMRI in subsequent sleep was used by Mascetti et al. to characterize links between local learning and NREMS [40]. An increase in regional cerebral blood flow coupled with the initiation of EEG slow waves in the local brain region was observed. The authors concluded; “These results provide an example of local sleep in which local initiation of slow waves during NREMS predicts later skill improvement…”. Similarly, PET techniques were used to examine comparable local changes induced during waking influencing subsequent localized metabolic changes during REMS. Human subjects were trained to perform a series of reaction time tasks prior to sleep. During subsequent REMS, increased metabolism occurred between the left dorsal premotor cortex and the pre-supplementary motor area [41,42]. Collectively, these studies provide good evidence that changes in waking localized blood flow/metabolism alters subsequent localized sleep. Incidentally, some sleep regulatory molecules, e.g., nitric oxide, are key regulators of cerebral blood flow.

The concept of localized sleep offers a potential explanation for the disconnect between insomniac patients' perception of not having sufficient sleep and their measured sleep obtained in sleep clinics [15]. Using ^{18}F-fluorodeoxyglucose PET, Buysse and colleagues described a high metabolic rate in the precuneus during resting wakefulness [43]. This area is posited to have a role in consciousness and state awareness. Glucose metabolism remained high during NREMS in insomniac patients, suggesting this area, and the perception of being awake, remained in a wake-like state [15].

Animal studies

Pigarev provided evidence for sleep being a property of local cortical networks in behaving monkeys [44]. He measured firing patterns of neurons in the visual cortices as they fell asleep while performing a visual task. As the monkeys fell asleep, some of the neurons stopped firing. Those neurons were found within the outer edges of the visual receptive field being engaged by the task. As the animals progressed into deeper sleep, neurons in the more central parts of the visual receptive field stopped firing. The topographical order of the systematic reduction in neuronal firing while falling asleep suggests local network control. The authors concluded that sleep is a property of local networks.

In a series of elegant studies, Rector characterized the sleep-like behavior of rat cortical columns *in vivo* [45,46]. He stimulated facial whiskers by twitching them or used auditory sounds to activate afferent neurons to the somatosensory or auditory cortex. He electrically isolated single cortical columns by placing an electrode array over either cortical area, then measured changes in cortical surface electrical potentials following twitches or sounds. Using signal averaging techniques, the evoked response potential

(ERP) was derived for the column receiving the enhanced afferent input. First, he replicated findings in the literature by showing that, on average, ERPs are higher during NREMS than during waking. He then determined the spontaneous states of multiple columns. When the rats were awake most, but not all, of the columns had low magnitude ERPs. In contrast, when the rats were asleep, most of the columns manifested ERPs of greater magnitude. A clear conclusion from this work was that, when the animals were behaviorally awake, parts of their brain could be asleep and vice versa. If cortical columns were intensively stimulated, or were spontaneously in the wake-like state, the probability of their entry into the sleep-like state increased the longer the stimulation, or wake-like state persisted. These data demonstrate sleep homeostasis within the local cortical network. They also show activity-dependency of transition into the sleep-like state. He extended these studies to show that single cortical column state can affect behavior. Thus, he trained rats to lick a sweet solution when a specific whisker was stimulated, but not when other whiskers were stimulated. Then he determined the task error rate in awake animals after whisker stimulation. If the ERPs in the cortical column receiving afferent input from the whisker used to train the animal to lick were low, thereby indicating the column was in the awake-like state, the rats did not make mistakes. In contrast, if the ERPs were high, indicating the column was asleep, then errors of omission and commission were made [3,15,47]. These behavioral data strongly suggest that the cortical column sleep-like state is indeed a local sleep state.

The ramifications of the Rector ERP/behavioral studies are large. For example, they provide a new way of viewing fatigue-induced poor performance [48]. Thus, some of the multiple small networks engaged in complex behavior could be entering the sleep-like states. If sufficient numbers of task-engaged networks are in the sleep-like states, the probability of errors increases. Collectively, Rector's work has provided very strong experimental evidence for sleep being a fundamental property of small networks *in vivo*.

Vyazovskiy, using independent techniques in adult rats, extended and amplified Rector's findings by showing that changes to sleep-like slow wave firing patterns occur in local cortical networks, both during natural or enforced sleep deprivation, as well as immediately upon normal, unprompted waking [49–51]. Moreover, indicative of sleep homeostasis, longer waking periods increased the frequency of slow waves and both the intensity and synchronicity of neuronal activity, as well as the propensity for different populations or circuits of cortical neurons to suddenly turn "OFF" [50]. Subsequently, recordings of both local field potentials and local multi-unit activity in rat frontal motor cortex after 4 h of sleep deprivation showed that EEG slow waves were larger and more frequent with sporadic and brief OFF periods toward the end of sleep deprivation as compared to the beginning. In fact, the numbers of OFF periods while awake significantly increased from the beginning to the end of the sleep loss period, suggesting that sleep pressure induced these sleep-like states in various populations of cortical neurons. Additionally, these sleep-like states lacked synchrony across the cortex, with some populations seemingly remaining "awake" as other populations "slept" [51]. Although there were no corresponding outward physical manifestations of these sleep-like states in the sleep deprived rats, performance in an assigned reach test was impaired when there was at least one OFF period, or if OFF periods occurred frequently, immediately before the task [51]. Specifically, after sleep deprivation, some populations of neurons in intact rat frontal motor cortex would "sleep" while other populations remained "awake", and decreased performance was associated with this sleep during wake brain activity [51].

In vitro studies

*In vitro*studies provide further evidence for local sleep by demonstrating that cortical cultures exhibit short bursts of spontaneous activity closely resembling the sleep signature of an intact brain [52,53]. This sleep-like behavior is the default state of *in vitro* cortical networks and is driven by glutamatergic receptors, though cholinergic receptors may also be recruited in some situations, as demonstrated by blockade of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors and kainate receptors [52,54]. TNF, a sleep regulatory substance, is involved in homeostatic glutamate receptor trafficking responsible for synaptic scaling [55] and drives cortical cultures into a deeper sleep-like state as indicated by higher electrical slow wave amplitudes [56]. In contrast, *in vitro* cortical networks can be "awakened" either by electrical stimulation or administration of excitatory neurotransmitters or their agonists [52–54,56–59]. Additionally, and like *in vivo* subjects, cortical cultures exhibit sleep homeostasis in response to "waking" stimuli [56] and do so in a correspondingly dose-dependent manner [59]. Gene expression in cortical cultures after excitatory cocktail stimulation induced changes in many genes previously linked to sleep deprivation *in vivo* [53]. Further, phosphorylation of the glutamate receptor component GluR1 increases after excitatory stimulation *in vitro*, mimicking *in vivo* studies that showed synaptic changes occur in sleep and wake states. Interestingly, neuronal TNF (and IL1) expression is enhanced by increased afferent input *in vivo* (Fig. 1) [60] or by optogenetic stimulation of neurons *in vitro* (Fig. 2) [56]. TNF, as mentioned, is involved in glutamate receptor dynamics. Finally, changes to metabolic pathways *in vitro*, as determined by metabolite measures, resemble sleep-linked metabolic changes found in animal studies [53].

Sleep and plasticity are mechanistically linked

There are very large literatures implicating IL1 and TNF in sleep regulation and they are extensively reviewed elsewhere

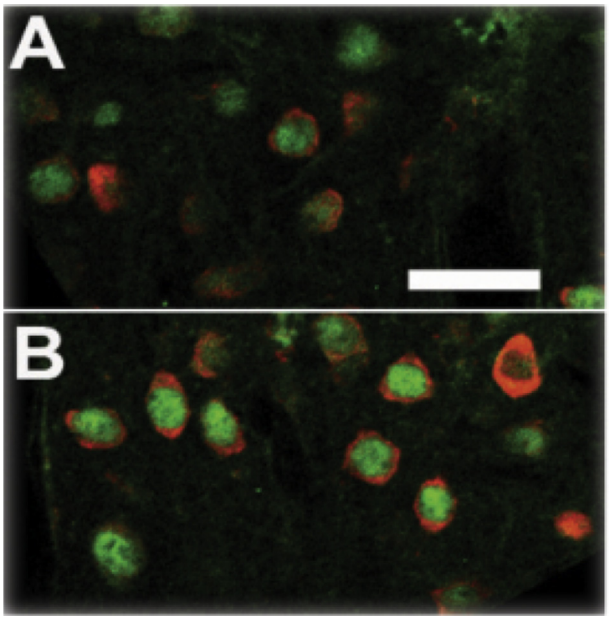

Fig. 1. Cortical somatosensory neuronal TNF is activity-dependent. Green nuclear staining is c-FOS and red cytoplasmic staining is tumor necrosis factor (TNF). A) From side of brain that received afferent input from whiskers that were not stimulated. B) From side of brain receiving afferent input from whiskers stimulated for 90 min before sacrifice. From Churchill et al., 2008 [60].

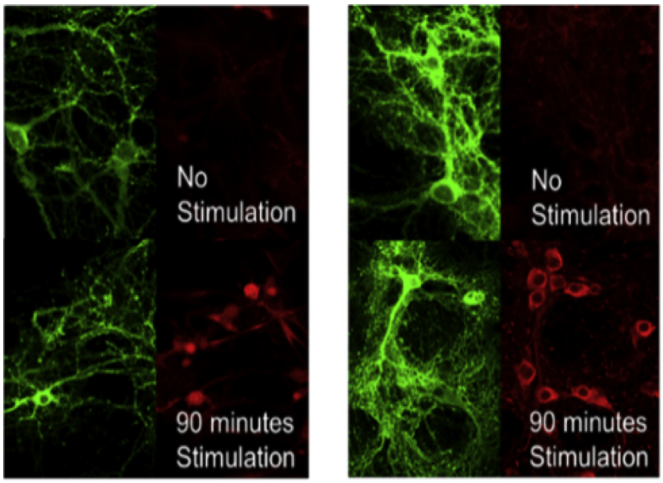

Fig. 2. Optogenetic stimulation induces IL1 expression in neurons. Left figures show c-FOS expression with no stimulation or after 90 min of optogenetic neuron stimulation. Right figures show interleukin-1 (IL1) expression with and without 90 min of stimulation. Light stimulation induced c-FOS nuclear expression as previously reported and it induced cytoplasmic IL1 expression after 90 min. Similar results were obtained when tumor necrosis factor (TNF) expression was measured only it was enhanced after 30 min of light stimulation and was back to baseline values by 90 min. Adenosine triphosphate (ATP) levels were also measured in the media; they increased after 30 and 90 min [56]. No responses to light stimulations were observable in Channelrhodopsin-2-negative networks.

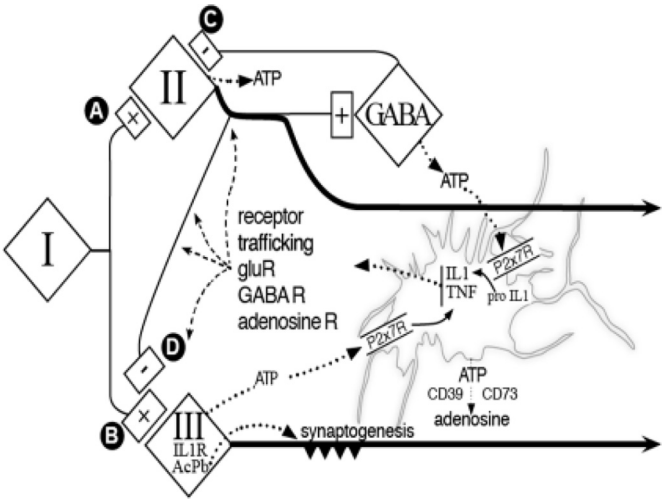

Fig. 3. Local actions within small circuits link cell activity to adenosine triphosphate (ATP) and sleep regulatory substance release to receptor trafficking, synaptic efficacy and synaptogenesis. Neurotransmission (neurons I, II and III) and gamma amino butyric acid (GABA)-labeled neurons and glia (illustrated by the irregular cell) excitation is associated with ATP release. ATP in turn, is rapidly degraded to adenosine via cluster density (CD) 39 and CD73. ATP also affects glia processing and release of interleukin-1 (IL1) and tumor necrosis factor (TNF). ATP, IL1, and TNF are well-characterized sleep regulatory substances. IL1 and TNF have multiple actions on neuromodulator (e.g., adenosine) and neurotransmitter (e.g., glutamic acid (glu) and GABA illustrated) receptor trafficking. Those changes lead to homeostatic synaptic scaling events. For example (see text as well), the neuron-specific IL1 receptor accessory protein is required for sleep homeostasis occurring after sleep deprivation [106] and is involved in synaptogenesis [105]. The black circles containing letters label synapses. A and B are excitatory synapses from cell I to cells II and III. C represents a GABAergic inhibitory input on neuron II. D represents presynaptic inhibition of synapse B. Receptor trafficking would lead to altered feedforward and feedback dynamics. As a consequence, oscillations within such small neuronal/glial networks result. It is posited that synchrony of multiple such networks lead to state oscillations of larger brain components, e.g., cortical columns as well as the entire brain. Synchronization of small chemically and physically linked networks leads to emergence of new properties, e.g., sleep [108–110].

[3,14,15,61–63]. Briefly, IL1 and TNF enhance sleep and EEG slow wave amplitudes; their inhibition leads to sleep inhibition; their expressions in brain correlate with sleep wake cycles and are enhanced by sleep deprivation; and pathologies with enhanced IL1 or TNF are associated with sleep changes. IL1 and TNF act on known sleep regulatory circuits, e.g., IL1 enhances hypothalamic sleep active neurons [64]. In healthy humans, blood levels of TNF correlate with EEG slow wave power [65]. After sleep deprivation, circulating levels of the 55 kDa soluble TNF receptor, but not the 75 kDa TNF soluble receptor, increase [66,67]. The TNF 55 kDa soluble receptor is a component of normal cerebrospinal fluid [68]. There are several other literatures linking IL1 and TNF to additional higher order brain functions such as learning and memory [69,70], fever [71], appetite [72], host defenses [73,74], and brain development [75].

A large literature connects neuronal activity to plasticity and the activity-dependent molecules involved. These molecules include all well-characterized sleep regulatory molecules including IL1 and TNF [3,15]. The activity-dependent expression of IL1 and TNF in brain is briefly described above (Figs. 1 and 2). More generally, IL1 and TNF are up-regulated in brain after excessive stimulation as occurs during kindling [76,77], sleep deprivation [78–81], after whisker stimulation in the somatosensory cortex (Fig. 1) [82,83], or during brain inflammation [84]. One mechanism linking cell activity to IL1 and TNF expression/release involves extracellular adenosine triphosphate (ATP). ATP is co-released with neurotransmitters [85,86] and acts via purine type 2 receptor ×7 to induce the release of IL1 and TNF [87,88] (Fig. 3).

There is another literature linking IL1 and TNF to brain synaptic receptor trafficking (already mentioned for TNF), synapses, neuronal excitability, and glial function. IL1 is involved in synaptogenesis [89], synaptic activity [90,91], cortical neuron migration [92], enhancing (low physiological amounts of IL1) or inhibiting (high pathological amounts of IL1) learning and memory and long-term potentiation (LTP) (reviewed elsewhere) [93–95]. Collectively, these literatures strongly implicate TNF and IL1 in sleep regulation, plasticity and other brain functions. Here we focus on their potential sleep regulatory roles in smaller parts of the brain.

IL1 and TNF enhance sleep-like states in parts of the brain *in vivo*. Unilateral application of TNF or IL1 onto the surface of the somatosensory cortex induces unilateral state-dependent increases in EEG slow wave power suggesting that one side of the brain can exhibit deeper NREMS than the other [96,97]. Conversely, unilateral cortical application of the soluble TNF receptor reduces EEG slow wave power during NREMS [46,96]. Unilateral application of a TNF small inhibitory RNA onto the surface of the somatosensory cortex reduces ipsilateral spontaneous cortical expression of TNF and EEG slow wave power during NREMS, but not during wake or REMS periods [98]. Similarly, unilateral application of IL1 to the surface of the somatosensory cortex ipsilaterally enhances EEG slow wave power during NREMS, but not during REMS or W [99]. Further, sleep deprivation-enhanced EEG slow wave amplitudes are inhibited if an IL1 soluble receptor is applied to the somatosensory cortex. Local application of other sleep regulatory substances onto the surface of the cortex, e.g., growth hormone releasing hormone [100,101] and brain derived neurotropic factor [102], also enhances EEG slow waves ipsilaterally.

At the single cortical column scale, Churchill et al. extended Rector's work to application of TNF onto the surface of the somatosensory cortex then stimulated a facial whisker and determined the subsequent amplitudes of ERPs [60]. TNF enlarged the

ERPs suggesting at the cortical column level the sleep-like state is enhanced.

In vitro tissue culture studies also support the idea that IL1 and TNF act locally to alter sleep-like states. Thus, IL1 signals through its type I receptor. The IL1 type I receptor is found in neurons and astrocytes and both cells mediate IL1-induced sleep [103]. The IL1/IL1receptor complex requires an accessory protein (AcP) to signal [104,105]. In neurons, there is an isoform of AcP, called AcPb. Mice lacking AcPb fail to exhibit a sleep rebound after sleep deprivation [106]. If cells from AcP knockout mice or from AcPb knockout mice are grown on MEAs, emergent electrical properties such as slow wave power and synchronization of electrical activity between electrodes develop more slowly in the AcPb knockout cells and more rapidly in the AcP knockout cells when compared to wild type cells [107]. AcP and AcPb knockout cells also show differential responsiveness to IL1 in culture. In similar studies using wild type cells, Jewett et al. showed that TNF induces a deeper sleep-like state *in vitro* [56].

Local to global sleep

The brain has many local networks including cortical columns which are intensely studied due to their accessibility. Cortical columns are biochemically and electrically coupled to each other such that they may synchronize states with other cortical columns and local networks that are in close proximity via chemical or electrophysiological signaling [3,15]. Even without top-down regulation, spontaneous oscillatory synchrony of small, coupled networks is widely observed in nature [108]. We proposed that organism sleep can occur as a consequence of spontaneous state synchronization of multiple local networks [2]. Additionally, *in silico* results of mathematical models suggest that local synchrony, including synchronous sleep-like states, occurs between closely situated small networks [59,110]. Moreover, as mentioned, sleep-like EEG slow waves can be enhanced locally in the cortex through application of somnogenic substances and that this is also followed by increased neuronal activity in the hypothalamic sleep regulatory areas [99]. Thus, local network synchrony of sleep-like states alone may lead to global sleep. However, such synchrony is likely modified by known sleep regulatory circuits to affect whole brain states.

Conclusion

Sleep has long been treated as a whole brain phenomenon regulated by sleep regulatory circuits (top-down regulation). Although this paradigm remains operational, its many anomalies led to a more inclusive paradigm that embraces the concept of sleep being a fundamental process of any viable neuronal/glial network. The newer view has greater explanatory value than the top-down regulatory paradigm. Thus, the local "bottom-up" view provides explanations for sleep walking, sleep inertia, sleepiness, and the poor cognitive and performance errors associated with prolonged wakefulness [48]. The new paradigm gained credibility via demonstrations that no individual part of the brain is required for sleep. Further, molecular mechanisms link sleep to plasticity and inflammation, reinforcing the concept of local sleep. Plasticity and inflammation are local and use-dependent phenomena that alter sleep and are altered by sleep, yet, like sleep, have emergent whole-body functions. Supporting evidence from human and animal studies support the hypothesis that sleep is initiated within small networks as a consequence of their prior activity. *In vitro* studies of cortical cultures provide additional evidence that any viable neuronal/glial network, whether *in vivo* or *in vitro*, exhibit sleep-like characteristics. The application of the local sleep concept to the clinic is just beginning.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Practice points

1) Localized waking and sleep states occurring simultaneously can provide explanations for many clinical observations such as insomnia, poor performance, sleep inertia, disassociate states, and sleepiness.
2) Use-dependency of state initiation suggests potential clinical approaches to sleep issues, e.g., intense localized brain stimulation.
3) Developmental changes in the sleep EEG may arise from maturation of synchronization mechanisms needed to coordinate local sleep states, e.g., a flat EEG during neonate quiet sleep to high amplitude delta waves during NREMS in adults.
4) The molecular regulatory mechanisms for sleep, inflammation, and plasticity are shared with each other; brain pathology of one is likely to affect the others.

Research agenda

1) Expansion of *in vitro* sleep studies to determine how simple networks synchronize state with each other.
2) Linking local sleep to metabolism in terms of molecular regulation and timing to answer the question of whether changes in local cerebral metabolism are driving sleep. Simple *in vitro* studies using different temperatures may help this endeavor.
3) Expansion of sleep and plasticity molecular mechanisms research. Exactly how are they linked? Is it possible to separate them? How are they linked at higher tissue organization levels? How do those linkages affect emergent outcomes?
4) Is local sleep similar during NREMS and REMS in different parts of the brain?
5) Are the sleep disruptions experienced by the aging linked to local sleep? And are they adaptive, e.g., playing a "night-watchman's" role?
6) What is the relationship between brain circadian peripheral clocks (outside the suprachiasmatic nucleus), cell-autonomous clock genes, and local sleep mechanisms?

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