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Hypothesis

Cellular Stress, Energy Constraints and the Energy Allocation Hypothesis of Sleep

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Abstract: A growing body of literature demonstrates a critical role for sleep in upregulating diverse biological processes related to protein synthesis, immune function, and cellular housekeeping such as intracellular transport and membrane repair. The energy allocation (EA) hypothesis places sleep in a broader context of resource optimization where sleep–wake partitioning of metabolic operations optimizes resource utilization. The EA hypothesis of sleep carries important implications in health, disease, and homeostatic mechanisms. Specifically, conditions that lead to cellular stress, energy constraints or depression of neuronal activity, such as epilepsy, ischemic stroke or cortical spreading depression, are here proposed to follow similar conserved processes that favor sleep. This review examines the role of local mechanisms, including cytokine release or the accumulation of adenosine, in downregulating wakefulness to favoring sleep, loss of functional connectivity and the upregulation sleep-coupled processes that promote survival.

Keywords: sleep function; energy allocation hypothesis; epilepsy; stroke; cortical spreading depression; cellular stress

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1. Introduction

The energy allocation (EA) hypothesis of sleep has been proposed as a unifying theory to understand sleep function and the diversity of its expression across species [1–3]. Basic concepts of the EA hypothesis also provide important insights into the role of sleep in health and disease. This brief communication considers implications of the EA hypothesis regarding the role of cellular stress, increased metabolic demands and energy constraints as a driver of sleep expression and the potential role for sleep in recovery processes.

2. Resource Optimization and the Energy Allocation (EA) Hypothesis of Sleep

The EA hypothesis proposes that diverse biological functions have evolved to couple with either sleep or wakefulness in both brain and periphery to promote resource optimization and survival [1,4,5]. Indeed, across species, a great diversity of genes are differentially expressed during either sleep or wake, with similar patterns in both brain and periphery [6–10]. Transcripts upregulated during waking are involved in energy metabolism, response to cellular stress and transcription activation, whereas those for sleep regulate protein synthesis, immune function, and cellular housekeeping such as intracellular transport and membrane repair, among others [7,10]. More recent data suggest that although transcription may largely be driven by the circadian clock, translation of mRNA into protein is coupled to the state of sleep [11].

The role of state-dependent metabolic partitioning as the foundation of sleep–wake alternation has remained underappreciated in the broader context of sleep function. For

example, sleep has long been hypothesized as a mechanism to conserve energy [12]. However, calculations regarding the amount of energy conserved by sleep had previously relied only on the amount of metabolic rate reduced during the sleep phase. Given that the whole-body metabolic rate decreases by approximately 15–30% during sleep compared to quiet wakefulness, an 8 h sleep quota had been suggested to provide approximately 7–9% total energy savings [13]. However, more recent mathematical modeling suggests that a partitioning of metabolic processes according to state promotes energy conservation beyond that achievable through metabolic rate reduction alone [4]. These calculations suggest that the total energy savings afforded an 8 h sleep quota may be 4-fold greater than prior estimates when considering the combined contributions of both metabolic rate reduction and state-dependent metabolic partitioning.

Mathematical modeling further shows that maintenance of waking-related processes during behavioral sleep would otherwise constrain the ability to partition functions according to state [4]. Stated more simply, downregulating waking-related functions during sleep enhances the ability to upregulate sleep-coupled processes, thus increasing energy savings derived through state-dependent metabolic partitioning. Finally, the ability to partition functions by state to the whole organism, including peripheral tissues, amplifies the total energy savings beyond what a single organ or structure could achieve. These basic principles have major implications for understanding the role of sleep in both health and disease.

3. State-Dependent Metabolic Partitioning and Homeostatic Responses

The partitioning of metabolic processes according to state carries important implications with respect to homeostatic processes driven by either sleep loss or energetic constraints. Sleep homeostasis refers to an increase in sleep duration and intensity following a period of sleep loss once an opportunity to sleep is given. The intensity domain is characterized by an increase in the amplitude of electroencephalographic (EEG) slow waves during non-rapid eye movement (NREM) sleep [14,15]. Slow-wave activity, also referred to as slow-wave energy, dissipates in a non-linear fashion during recovery sleep, consistent with a homeostatic response.

The EA hypothesis posits that the separation or partitioning of metabolic processes according to either sleep or wake creates a debt cycle, representing unfulfilled biological operations normally coupled with sleep, and plays an important role in modulating the homeostatic sleep response [1,4]. Not only may the unfulfillment of sleep coupled processes contribute to cellular dysfunction, but the EA hypothesis goes further. Specifically, elevations in the debt cycle are hypothesized to trigger a reactive homeostasis, driving unfulfilled biological processes to decouple from sleep and to upregulate, instead, during waking to maintain organism integrity during periods of sleep loss [1].

The concurrent fulfillment of both wake-related and sleep-related processes during prolonged waking or chronic sleep restriction is proposed to overtax cellular infrastructure capacity, leading to increased cellular stress, misfolding of proteins within the endoplasmic reticulum, and increased energy demands, leading to increased adenosine, AMP and phosphorylation. These intermediary products then signal, through various mechanisms, the increased drive to sleep and an inhibition of waking mechanisms [16–19]. These same processes, however, also occur during metabolic constraints independent of sleep deprivation, demonstrating conserved mechanisms by which intermediary products such as adenosine may terminate wake and favor sleep.

Extreme and persistent sleep loss presents a particular challenge when specific biological processes normally coupled with sleep cannot be fulfilled. For example, experimental sleep loss impairs skeletal muscle protein synthesis [20,21], leads to decreased bone formation with reduced osteoblast activity and a shift to bone resorption [22], and impairs immune responses normally coupled to sleep [23], just to illustrate a few such effects. Indeed, mathematical modeling demonstrates non-linear rises in the debt cycle with extreme sleep loss which may represent an escape from homeostasis, potentially leading to

more extreme pathology or even death. Finally, given that both brain and periphery are hypothesized to partition metabolic processes as a function of behavioral state, the signal for a homeostatic sleep response could originate from any tissue and is not restricted to the brain. This latter concept is highly theoretical but is a prediction of the EA hypothesis. In support of potential peripheral contributions, recent data demonstrate several pathways by which skeletal muscle may regulate sleep amount following sleep loss. These include expression of the circadian clock gene Bmal1 in skeletal muscle or other muscle-to-brain signaling pathways via myokines and myometabolites [21,24,25].

4. Cellular Stress and Energy Constraints

Numerous canonical metabolic cascades are triggered by perturbations in cellular homeostasis or cellular stress for which the state of wakefulness, particularly extended waking, can be a trigger. Indeed, early studies identified the upregulation during waking and the downregulation during sleep of genes in the cerebral cortex that respond to cellular stress, such as heat shock proteins and molecular chaperones [26]. For example, BiP (Binding immunoglobulin Protein) is a molecular chaperone within the endoplasmic reticulum (ER) that is released when unfolded proteins accumulate during periods of cellular stress and energy constraints [27,28]. In stable conditions, PERK (protein kinase RNA (PKR)-like ER kinase) and ATF6 (activating transcription factor 6) are bound to BiP in the ER membrane, keeping them inactive. When unfolded proteins accumulate in the ER, BiP is released from these complexes to aid in the folding process. The release of PERK and ATF6 from BiP leads to their activation, inducing further signal transduction events to counteract the accumulation of unfolded proteins [27].

Interestingly, prolonged wakefulness or short-term sleep deprivation is associated with an increase in BiP expression in the brain of rodents, birds and Drosophila, suggesting an evolutionarily conserved response to prolonged wakefulness [7,10,26,28,29]. In addition, sleep loss leads to increased oxidative stress in peripheral organs, including oxidative DNA damage and cell injury in the liver, lung and small intestine [30]. Recent work demonstrates the role of mitochondrial reactive oxygen species in triggering homeostatic sleep responses in Drosophila [31]. Taken together, wakefulness is a state of increased cellular stress, but the cellular stress of prolonged wakefulness or sleep deprivation is even greater.

Organisms that partition metabolic processes according to behavioral state would be expected to favor the state that increases survival during periods of disease or pathology. Given that biological functions in both the brain and periphery related to cellular housekeeping, immune function, growth and repair are typically coupled to the state of sleep and that the high energy costs of wakefulness could otherwise limit resource availability, it is not surprising that sleep should be favored during times of disease or the associated cellular stress [1]. Indeed, it is now well established that disease, through cytokine production and other intermediaries such as tumor necrosis factor alpha, markedly increase sleep expression, including both sleep duration and slow-wave activity [23,32,33]. In the EA hypothesis of sleep, the favoring of sleep during such pathological conditions is viewed as an adaptive response independent of prior sleep need where increases in sleep quota or sleep intensity occur secondary to cellular stress and energy constraints to promote survival [1].

4.1. Learning, Neural Plasticity, Energy Demands and Increased Sleep Need

An increase in sleep intensity or duration, independent of prior sleep loss, can be observed not only during disease states, but also following conditions that increase cortical activation or central nervous system metabolic demands. These sleep responses are manifested by increased local cortical slow-wave activity reflecting prior waking experience such as learning [34]. These responses are often interpreted with respect to the synaptic homeostasis (SHY) hypothesis [34,35]. Specifically, the waking state is associated with global synaptic potentiation driven by waking-related experiences. The increased synaptic load carries an energetic cost and may limit new synapse formation secondary to

space and energy constraints. In the SHY hypothesis, cortical slow-wave activity during sleep is viewed as a mechanism to downscale synaptic load. The global reduction in synapses during slow-wave sleep results in an improved signal-to-noise ratio where more recent synapses are relatively preserved, and overall energy demands related to synaptic maintenance are reduced.

Although the role of metabolic processes associated with learning and synaptic plasticity in driving subsequent sleep is poorly understood, numerous mechanisms have been postulated. For example, brain-derived neurotrophic factor (BDNF) is rapidly transcribed following long-term potentiation (LTP) and is increased during wakefulness associated with learning or during sleep deprivation [36]. BDNF has been demonstrated to increase slow-wave activity during subsequent sleep bouts, even in a locally dependent manner, and to play an important role in neural plasticity [36,37]. Other mechanisms associated with waking, such as phosphorylation or local adenosine accumulation, can also promote both sleep intensity and duration [16–19]. These and related mechanisms provide a link between waking-dependent activity and subsequent sleep responses.

A classic example of how learning during waking can impact subsequent slow-wave activity during sleep was demonstrated in human subjects learning a motor task prior to bedtime [38]. In this study, subjects manipulated a handheld cursor to reach for visual targets requiring either systematic rotational adaptations that require learning or, instead, similar cursor movements without rotations. The two conditions require similar kinematic motor activity, but only the rotational learning adaptation activates the right parietal cortical areas. The authors show that when comparing the two conditions, only the rotational motor learning task involved an increase in right parietal slow-wave activity during subsequent sleep. Moreover, those who showed the greatest local slow-wave activity demonstrated the greatest learning effects. Since the overall motor movements required during both conditions were similar, the increase in slow-wave intensity could not be attributed to a general motor-induced fatigue. A follow-up study from the same group demonstrates that immobilization of the arm during the day in human subjects leads to a significant decrease in slow-wave activity of corresponding cortical areas during subsequent sleep [39]. Although cortical metabolic activity was not measured in these studies, these data clearly show that local sleep intensity can be modulated by waking activity independent of prior sleep loss.

In the EA hypothesis of sleep, synaptic downscaling as described in the SHY hypothesis is one of many biological processes specifically upregulated during sleep. Synaptic modulation is an energy-consuming process for which resources must be allocated. Maintaining a waking state constrains the ability to downscale synapses according to the SHY hypothesis [35]. From an EA hypothesis perspective, shutting down wakefulness improves the efficiency of synaptic modulation and thus promotes resource optimization, similar in concept to that suggested by mathematical modeling for any process specifically coupled to the state of sleep [4].

4.2. Metabolic Constraints Induced by Epileptic Seizures and Ischemic Stroke

An open question is to what extent cortical metabolic constraints from pre-sleep behaviors may also subsequently contribute to either the local or global effects of sleep intensity or duration. An extreme example of increased metabolic activity in the brain that can increase slow-wave activity is that following an epileptic seizure. Indeed, the local EEG slowing observed following seizure activity demonstrates similar characteristics to slow-wave sleep [40]. For example, a recent study evaluated functional network dynamics from EEG signals during wakefulness to deep sleep transitions of volunteers compared with pre-seizure to post-seizure transitions of patients suffering from focal epilepsy [40]. An analysis of global network dynamics demonstrates a loss of functional network connectivity during transitions from both wake-to-sleep and pre-seizure-to-post-seizure conditions. One interpretation is that functional disconnection associated with sleep may allow for local synaptic downscaling in brain areas particularly activated in wakefulness.

Ischemic stroke provides another example. Here, a necrotic core is often surrounded by an ischemic penumbra where energetic constraints limit normal cellular functioning but where recovery of normal cellular function is possible [41]. The ischemic penumbra is typically characterized by focal cortical EEG slowing. Interestingly, animal models demonstrate that interventions that favor sleep or cortical slow-wave activity during the acute phase of ischemia improve functional outcomes during recovery [41–43]. It remains to be determined if such interventions may promote the upregulation of sleep-coupled processes such as cellular housekeeping and protein synthesis.

Also unclear is whether similar metabolic processes may play a role in cortical spreading depression (CSD), an electrophysiological phenomenon involving a local depression of neuronal activity which can spread to adjacent areas and can be observed in association with numerous neurological disorders, including epileptic seizures, ischemic stroke, traumatic brain injury and migraine with aura [44,45]. CSD is characterized by a brief neuronal excitation followed by a long-lasting depression of cortical activity. Although the mechanisms of CSD are poorly understood, the relatively slow time course and local spreading of depression to adjacent topographical areas is consistent with local processes related to energy constraints and cellular stress.

The EA hypothesis provides additional theoretical perspectives regarding the role of slow-wave activity following increased cortical metabolic demands during waking. Functional disconnection related to the cortical slowing of either sleep, post-ictal events, or ischemia, for example, may also favor rapid shifts in resource allocations away from those coupled with waking to, instead, favor sleep-coupled biological processes. Indeed, increased pre-sleep cortical metabolic activity would be anticipated to increase cellular housekeeping requirements, functions normally coupled to the state of sleep. As would be expected, numerous physiological mechanisms have been described related to energy depletion, such as the accumulation of adenosine or consequences of cellular stress, which may act locally to shut down both neuronal activity and functional connectivity, thus favoring local homeostatic slow-wave responses. These local mechanisms would thus drive increased sleep intensity or duration as a function of pre-sleep metabolic constraints, representing an adaptive physiological response promoting homeostasis of cellular functioning.

5. Summary

The EA hypothesis proposes that energy savings through the partitioning of metabolic processes according to sleep or wakefulness promote resource optimization, presenting a unifying perspective of sleep function across species. The upregulation of cellular processes such as protein synthesis, intracellular transport and membrane repair places sleep in a unique position that is favored during disease or conditions of metabolic constraints that increase cellular stress. Indeed, the maintenance of a waking state during periods of cellular stress would otherwise increase metabolic demands while also constraining the ability to upregulate needed sleep-coupled operations. Finally, local metabolic or substrate demands induced through either learning or metabolic requirements may promote homeostatic processes at the local level through the release of adenosine or other intermediary products. Taken together, a growing body of literature demonstrates a critical role for sleep and its coupled functions in promoting health, recovery and neural plasticity. Understanding how sleep upregulates such processes is becoming an even greater focus for future scientific discovery.

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