

Review

The Function of Sleep

Daniel A. Barone ^{1,*} and Ana C. Krieger ²

¹ Weill Cornell Medical College of Cornell University, New York, NY 10065, USA

² Center for Sleep Medicine, Weill Cornell Medical College, New York, NY 10065, USA

* **Correspondence:** Email: dab9129@med.cornell.edu; Tel: +1-646-962-7378;
Fax: +1-646-962-0455.

Abstract: The importance of sleep can be ascertained by noting the effects of its loss, which tends to be chronic and partial, on cognition, mood, alertness, and overall health. Many theories have been put forth to explain the function of sleep in humans, including proposals based on energy conservation, ecological adaptations, neurocognitive function, neural plasticity, nervous system and physical health, and performance. Most account for only a portion of sleep behavior and few are based on strong experimental support. In this review, we present theories proposing why sleep is necessary and supporting data demonstrating the effects of inadequate sleep, with the intention of gleaning further information as to its necessity, which remains one of the most perplexing mysteries in biology.

Keywords: sleep; function

1. Introduction

Many theories have been proposed to explain the function of sleep in humans, most accounting for only a portion of sleep behavior; some based on strong experimental support. Proposals have been based on factors such as energy conservation, ecological adaptation, neurocognitive function, neural plasticity, nervous system and physical health, and performance, and yet the importance of sleep is most powerfully evidenced by the effects of its deprivation [1], in which cognition becomes impaired [2], mood becomes labile [1], and microsleep episodes, which are periods of temporary loss of consciousness, become apparent [1,3]. Despite the observation that 24 hours (h) of sleep deprivation does not bring about change in areas of brain affecting executive functions in healthy individuals [4], chronic and partial sleep deprivation is increasingly recognized as having deleterious effects on health [5]. In this review, we will briefly discuss the stages of sleep, as well as explore some of the theories proposing why sleep is necessary and present data demonstrating the effects of

disrupted or diseased sleep. While the evidence presented in some cases is conflicting, this fact points to the complexity of sleep mechanisms and sleep research, and the difficulties researchers have faced in answering these elusive questions.

2. The Origin of Sleep and Centers of Sleep Control

The proposed mechanisms for the origin of sleep are varied and include the classical concept of central sleep regulation by thalamocortical relays, the brainstem, and the hypothalamus [6–8]; local network regulation of sleep through sleep regulatory factors [9–11]; and decentral regulation involving cortical contributions [7,11] and states of individual cortical neurons being either active or inactive [12]. Thalamic neurons provide a state-dependent gating of sensory information based on their ability to produce different patterns of electrogenic activity during wakefulness and sleep [13], and are thought to provide an interface between these concepts through rhythmogenesis of sleep-related activity [14]. We will explore each of these mechanisms briefly.

The central regulators of sleep include the brainstem and the hypothalamus [14]. The brainstem actively maintains wakefulness via the reticular activating system and through sensory pathway activity [15]. The ventro-lateral preoptic nucleus of the hypothalamus was suggested to initiate sleep onset by several mechanisms of reciprocal inhibition of the cholinergic, noradrenergic, and serotonergic arousal systems in the brainstem [7], histaminergic systems of the tuberomammillary nucleus in the posterior hypothalamus, and cholinergic systems of the basal forebrain. All of these areas are modulated by the orexinergic arousal system of the lateral hypothalamus [16]. When active, these systems promote wakefulness, and accordingly, their inhibition promotes sleep [14].

Local network regulation of sleep involves biochemical mechanisms that keep track of past sleep-wake activity [11], accounting for a homeostatic element [10]. This homeostat is comprised of several sleep regulatory substances, such as adenosine which acts on thalamic and basal forebrain neurons to promote sleep [17], as well as growth hormone-releasing hormone (GHRH), tumor necrosis factor- α (TNF- α), and interleukin (IL)-1 β which act directly on hypothalamic preoptic neurons to promote sleep [18]. TNF- α and IL-1 β also act on the locus coeruleus [19] and IL-1 β additionally acts on raphe serotonergic neurons [20], and on GHRH-receptive γ -aminobutyric acid (GABA)-containing neurons in the hypothalamus [21]. These sleep regulatory substances are produced in response to cellular activity and metabolism, with sleep loss increasing IL-1 β , TNF- α , and adenosine levels. Additionally, brain-derived neurotrophic factor (BDNF) [22] is thought to play a key role in sleep regulation. The brain is able to induce activity-dependent oscillations relating to local sleep-like states of neuronal assemblies (e.g. cortical columns) and monitor past neuronal network activity to react with increased sleep or wakefulness as a result of these regulatory substances [11]. Sleep regulatory circuits thus may integrate information about the state of cortical columns with information about the time of day, sensory input, mental activity, or other determinants of a whole organism sleep-wake state [14].

Possible decentral mechanisms include glial processes and the release of adenosine and nitric oxide (NO) [14]. Increased neuronal activity increases extracellular adenosine concentrations throughout the brain [11], which ultimately decreases neuronal activity in the basal forebrain through A₁ adenosine receptors [11]. During sleep deprivation, it has been demonstrated that there is an increase of adenosine in cortical areas; this suggests a decentral regulation of sleep homeostasis [23] in which adenosine acts as a sleep-inducing factor [17,23]. Adenosine also promotes sleep by inhibiting

the histaminergic neurons in the tuberomammillary nucleus [24] and affecting sleep-related electrical activity in the thalamus [14]. Another potential decentral mechanism is gaseous NO formation [14]. Because of its volatile nature, the actions of NO are local and vary depending on the brain structure involved [14], and has been shown to stimulate the accumulation of adenosine [25]. Furthermore, thalamocortical dynamics and their modulation by the ascending arousal system and locally released neurochemicals are also affected by glial cells [26].

Sleep is characterized by synchronized events occurring in the thalamocortical system [27], which is comprised of the cortex, the nucleus reticularis thalami (NRT), and the dorsal thalamus [27]. Oscillations, typical of sleep states, are generated through synaptic interactions between three major cell types [27]: GABA-containing neurons of the NRT, thalamocortical relay neurons, and cortical pyramidal neurons [14]. Sleep homeostasis of neuronal assemblies, through the action of adenosine, for example, can also be found in thalamic neurons [14]. While future research is still needed, it is thought that both central and decentral regulators must target the thalamus in order to induce whole organism sleep [14].

3. Rapid Eye Movement (REM) and Non-REM (NREM) Sleep

Sleep is defined in the laboratory by recording the electrical activity of large groups of cortical neurons and muscle cells using standardized scoring criteria and pre-determined recording locations on the scalp. These polysomnographic (PSG) recordings are utilized to define the states of wakefulness and sleep. During wakefulness, low-voltage fast electroencephalogram (EEG) activity and high muscle tone are seen. Sleep-related EEG activity varies depending on the stages of sleep. Rapid eye movement (REM) sleep consists of low voltage fast activity in combination with a complete loss of muscle tone (REM muscle atonia) and characteristic rapid eye movements, while non-REM (NREM) sleep is characterized by high-amplitude low-frequency EEG, a reduction in muscle tone compared to wakefulness, and slow rolling eye movements [28]. In humans, NREM sleep is further classified according to standard criteria [29] into: Stage 1 NREM sleep (N1), exhibiting theta activity; Stage 2 NREM (N2) sleep, characterized by sleep spindles and K-complexes; and Stage 3 of NREM sleep (N3), exhibiting prominent, high-amplitude delta waves, noted as slow wave sleep.

Awakening from sleep necessitates the restoration of neuronal firing patterns necessary to re-create and sustain conscious wakefulness. Accordingly, it has been proposed that the brain uses REM sleep to help wake itself up after experiencing an adequate amount of sleep. The evidence for this theory includes the following:

- Upon falling asleep, the brain spends a large proportion of time in slow wave sleep and, as the night progresses, is interspersed with periods of REM that become longer and more frequent toward morning;
- Dreams resembling consciousness are a reliable component of REM sleep;
- The final awakening during a night's sleep usually occurs following a REM period;
- Both REM sleep and waking consciousness seem to arise out of a similar brainstem ascending arousal system;

- Sleep inertia [30,31], which is a temporary period of reduced alertness and impaired cognition occurring from an awakening out of NREM sleep, must be mitigated in preparation for wakefulness;
- Projections from the cortex to the brainstem arousal areas during REM sleep progressively raise the sleeping brain to the threshold required for wakefulness [32].

Time spent in REM sleep tends to correlate with the degree of brain maturity at birth, consistent with the view that REM sleep plays a major role in brain maturation [33]. Selective REM sleep deprivation results in increased attempts to enter REM sleep during wake, which is suggestive of the development of a REM sleep debt [34]. The question of why this state of sleep exists, during which time there is paralysis of skeletal muscles [35] is intriguing given the lack of a definitive answer as to the function of sleep in general.

In general, NREM sleep is considered to be the time during which the brain recovers from prior wakefulness [36], which is supported by data demonstrating extended wakefulness being followed by a compensatory increase in both NREM sleep time and intensity [37]. The intensity of NREM sleep is reflected in the amount of slow (delta) waves in the EEG [38,39], in that the longer the period of wakefulness is, the more slow wave activity is increased at the beginning of NREM sleep, which then gradually declines during the course of sleep as the NREM sleep debt dissipates [40–44]. The slow waves begin as slow oscillations emerging from local circuits, which then travel across the whole cortical surface as waves of activations and inactivations. This rhythmic oscillation in the corticothalamocortical network is fundamental for the maintenance of cellular and synaptic properties of the circuits as well as for sleep functions such as replay and memory consolidation [45]. Sleep inertia, as noted above, may be a manifestation of some neuronal assemblies remaining in the sleep-like state despite other assemblies having transitioned to the wake-like state and resulting in awakening; in other words, the degree of sleepiness may be a result of neuronal assemblies that are in the sleep-like state compared to the wake-like state [11]. Other studies have shown that slow wave activity during NREM sleep depends not only on the duration, but also on the quality of prior wakefulness in that the experience of stress may accelerate the build-up in sleep debt and increase the need for sleep [46,47].

4. Energy Conservation and Ecological Adaptations

4.1. Conservation of Energy

One of the most commonly cited theories on sleep function is that it conserves energy beyond what is attainable from quiet wakefulness [48]. This model has been viewed as a relatively passive process in which all biological functions are equally reduced during sleep, such as in hibernation [48–50]. However, the presence of REM sleep, and it being a state of increased brain energy metabolism, would appear to contradict this model. Furthermore, the amount of energy saved during sleep compared to wake is relatively minor, and thus some have argued that because this savings lacks profundity, it cannot be considered the *primary* function of sleep [51–53].

Additionally, it has been argued that the long sleep duration of children could be an energy conservation measure during ages with relatively high metabolic rates and at which time vital needs are attended to by others. Conversely, sleep duration declines with aging and can thus be considered to

correlate with the reduced metabolic rate and a consequent change in the trade-off between waking tasks and benefits of sleep [50].

4.2. Energy Allocation

This proposal is based on the evolutionary principle that all organisms have evolved to temporally allocate energy to basic functions such as growth, maintenance and reproduction from birth to death in a manner that maximizes reproductive output while meeting the energy constraints of the ecological niche [54]. In this proposal, there are three energy allocation strategies noted: sleep-wake cycling; torpor (i.e. hibernation or periods of reduced metabolic demand); and continuous or predominant wakefulness [54]. The evolutionary drive to expend energy in waking is performed at significant cost with respect to biological investment in terms of cellular repair, immune function, and neural network reorganization. Thus, sleep is a state during which energy reserves are used to replenish deficits resulting from being in the waking state and to prepare for the next bout of wakefulness. The expected cycling of wakefulness and sleep allows for this biological investment to be differentially allocated among behavioral states. Thus, sleep-wake cycling is thought to have evolved in order to optimize energy utilization conflict by means of reallocating energy demands to the various biological processes which would otherwise be competing, over the course of a circadian timeline [54].

4.3. Cellular Recovery/Repair

Several mechanisms proposed for the function of sleep can be viewed as processes aiding in the cellular repair of damage caused by metabolic processes, i.e that sleep is required for recovery, or provides some recuperative process [5,55,56]; but what is actually being recovered has remained elusive [51]. Endogenous clocks drive 24-hour rhythms of behavior and physiology and are regulated by a network of cellular oscillators; these are in turn controlled by a set of clock genes organized in a system of interlocked transcriptional feedback loops [57]. The act of sleeping can reverse sleep loss-induced changes in cellular metabolic status, and thus it has been proposed that the regulation of circadian clock genes by cellular metabolic sensors is an intermediate step between cellular metabolic status and sleep [58].

A large portion of genes in the brain change expression with sleep [59,60], and further analysis has shown that sleep-associated transcripts encoded proteins involving the synthesis of complex macromolecular components, intracellular transport, and endo/exocytosis [60]. Wake, in contrast, is associated with the regulation of genes involved in transcription and RNA processing and increased expression of molecular chaperones, a finding suggesting cellular stress [60,61]. Taken together, this mechanism suggests sleep as a function to restore macromolecules [60] and replenish/traffic transmitter vesicles used by extended wakefulness. A strength of this restoration hypothesis is that it being cellular-based, is applicable to all organisms and tissues, and suggests that sleep is helpful to reverse cellular changes that occur during wakefulness [5]. Other data demonstrating that protein synthesis is actually greater during wakefulness than sleep, and influenced by feeding [62–64], resulted in a refutation of the restorative hypothesis of sleep [53,65].

4.4. Adaptive Inactivity

It has been proposed that sleep should be viewed not as a vulnerable, maladaptive state that has persisted because it contains some unknown physiological function; rather, it should be considered a state that increases the efficiency of behavior through suppression of activity at times that have maximal predatory risk and reduced opportunity for meeting vital needs, and through permission of activity at times of maximal food availability and minimal predatory risk [50,66–68]. Efficiency is increased by reducing metabolism and muscle tone during periods of inactivity [50]. The inactivity, or “adaptive nonresponding” associated with sleep not only conserves energy [50], but also reduces the risk of injury and predation, ultimately viewed as a mechanism designed to keep an animal away from danger. However, sleep is oftentimes observed in even the most exposed and unsafe of sleeping sites, which suggests that the underlying necessity of sleep is greater than the relative safety otherwise offered through quiet wakefulness [51].

4.5. Oxidative Stress

It has been theorized that, during sleep, endogenous compounds accumulate and trigger antioxidative mechanisms [69]. An important antioxidant is glutathione, which reduces disulfide bonds formed in cytoplasmic proteins, thus preventing cellular damage by free radicals [70]. Intracerebroventricular application of oxidized glutathione demonstrated an increase in slow wave sleep, suggesting a modulatory effects on sleep stages [71]. Although it may serve as a sleep-inducing molecule, no sleep effects were found after its intravenous administration [72].

5. Neurocognitive Function, Neural Plasticity, and Nervous System Health

5.1. Neural Network Reorganization

Earlier theories of sleep were based on the assumption that it occurs at the level of the whole organism and governed by central control mechanisms. More recent evidence indicates that sleep might be regulated at a more local level in the brain, within small groups of highly interconnected neurons which exhibit altered input/output relationships [11]. Experimental findings suggest that growth factors, released locally acting in paracrine and autocrine fashions, induce the altered input/output relationships, and provide the structural basis for synapses. Thus, it has been theorized that neural induction of growth factors and their subsequent effects on input/output relationships cannot be separated from the growth factor-induced synaptic sculpturing that occurs during the sleep period [73]. Chronic sleep restriction likely induces long-term neuromodulatory changes possibly explaining why recovery from it may require more time than from acute sleep loss [74].

The synaptic homeostasis hypothesis argues the notion that sleep is the price the brain pays for plasticity, which is the ability of the brain to change its structure such as when memories are reorganized and reactivated [75]. The authors of this theory cite that during a waking episode, learning requires strengthening connections throughout the brain, which increases cellular needs for energy. During sleep, then, spontaneous neuronal activity renormalizes net synaptic strength and allows for the development and regression of neuronal spines, also restoring cellular homeostasis. Down-selection of synapses can also offer insight into the benefits of sleep on memory acquisition, consolidation, and

integration [76].

5.2. *The Glymphatic System*

It has been reported in mice that there exists a clearance system using convective flow between the cerebrospinal fluid and interstitial fluid to remove toxic metabolites from the brain; furthermore, the clearance activity of this so-called “glymphatic system” was found to be strongly stimulated by sleep [77]. The resulting clearance is associated with an increase in interstitial volume, possibly by shrinkage of astroglial cells. The induction of anesthesia can activate the glymphatic system to clear potentially neurotoxic proteins such as beta-amyloid (known to contribute to Alzheimer’s disease, AD). In fact, this clearance process is as much as two-fold faster in sleep than during waking hours [78], which heralds the possibility that glymphatic dysfunction may play a large role in the pathogenesis of neurodegenerative diseases as well as maintenance of cognition. Recent data suggests that quality and duration of sleep may predict the onset of AD [79,80], and that adequate sleep may reduce the risk of AD in apolipoprotein E ϵ 4 carriers [81]. It has been pointed out that further characterization of the glymphatic system in humans may result in new prevention and treatment strategies of neurodegenerative diseases. Thus, it has been suggested that a public health initiative to ensure adequate sleep may prove useful in preventing AD, particularly in carriers of apolipoprotein E [78].

5.3. *Memory and Cognition*

Further evidence suggests that sleep may benefit or facilitate learning/memory [82–87], and the importance of both REM sleep [87] and slow wave sleep [85] for brain function has been well documented. Sleep seems to be related to brain plasticity [88,89], and extensive research has supported the idea that sleep enhances one’s ability to learn and remember [86,90–92]. Particularly, sleep has been shown to enhance the ability to recall spoken language [93], spatial memories [94,95] auditory patterns [96], motor skills [91,97], and factual information [98,99].

Different types of memory may be enhanced by different types of sleep [100], and while there are exceptions to the patterns [85,101], the data is compelling. Whereas memories involved in performing a task such as riding a bicycle (i.e. procedural memories) may be enhanced by REM sleep [100], memories involved in remembering abstract ideas and facts (declarative memories) seem to benefit from slow wave sleep [102]. There exists data which does not seem to fit this paradigm; antidepressant drugs such as monoamine oxidase inhibitors reduce or eliminate REM sleep [103], and despite the widespread use of such drugs, there has been no evidence of marked disruptions to memory or learning [104]. In fact, it has been found that drug induced suppression of REM sleep had no effect on memory consolidation for word pairs and actually enhanced memory for finger-tapping skills [105]. Thus, it seems there is much yet to learn about the effects of sleep and memory [100].

5.4. *Mental Health*

Symptoms of insomnia commonly coexist with depression, however insomnia is more complex and may play a role in predicting depression incidence [106]. Meta-analytic data demonstrates that disturbed sleep results in a two-fold increased risk of depression [107], and is one of the first clinical

signs of a depressive disorder [108]. Persistent insomnia was demonstrated to result in a 14-fold greater risk of depression in a group of patients where it persisted beyond one year [109], and appears to be specific to those with a history of depression [110]. However, even in those without a depression history, persistent insomnia was found to predict risk for depressive symptoms over six years [111]. The addition of cognitive behavioral therapy for insomnia to standard antidepressant treatment generates a more rapid and durable remission of depression than does standard treatment alone [112]. Interestingly, total sleep deprivation alleviates depression [113,114], but the effects are rapidly reversed by sleep. Finally, it has been demonstrated that acute sleep deprivation increases risk-taking behavior [115–117] and impairs the ability to integrate emotion and cognition to guide moral judgments [118].

6. Physical Health and Performance

6.1. Cardiovascular Health

Whereas the cardiovascular changes that occur during normal sleep are beneficial, such as reducing cardiovascular activity throughout NREM sleep [119], sleep disturbance is very tightly linked to cardiovascular disease [120]. The effects of insufficient sleep on cardiovascular risk factors including blood pressure, glucose metabolism, hormonal regulation, and inflammation are well known and derived from studies utilizing experimental models of total and partial sleep deprivation [121]. Cardiovascular disease seems to affect those who report sleep complaints and/or have short sleep duration [122]. One recent meta-analysis of 11 prospective studies [123] demonstrated that short sleep duration, as well as complaints of sleep maintenance and early-morning awakening, but not difficulty falling asleep, predicted an increased risk of hypertension. Another systematic review [124] as well as a large-scale epidemiologic study [125] reported similar findings.

The role of insomnia complaints in combination with short sleep duration with regards to cardiovascular disease prediction has been examined by PSG in a study of more than 1,700 adults, and in those reporting insomnia for more than one year in combination with short sleep duration (≤ 5 h) had a five-fold greater risk of hypertension [126], with prospective findings demonstrating a four-fold increased risk of incident hypertension [127]. Additionally, a large nationwide study in Taiwan showed that clinically significant insomnia was associated with an increased risk of acute coronary syndrome [128]. Despite the data, not all studies have demonstrated a link between insomnia complaints and hypertension [129], and some have found none to modest associations when insomnia complaints are reported without the presence of short sleep duration [130,131].

Short sleep duration alone robustly affects risk of cardiovascular disease, similar to that of short sleep duration on inflammation [132–134]. Short sleep duration was associated with an increased risk of prevalent hypertension in a meta-analysis of 6 prospective and 17 cross-sectional studies [135]. Another meta-analysis reported that short sleep duration is associated with morbidity and mortality from coronary heart disease and stroke [136]. Sleeping less than 5 hours per night presents the greatest risk for cardiovascular events [137], although sleeping less than seven hours per night has been shown to increase the risk of cardiovascular mortality [138]. Extremes of sleep may contribute to cardiovascular disease, similar to the effects of sleep extremes on inflammation [135,136], as reported in 2 meta-analyses. It was found that long sleep duration was also associated with hypertension [135] and a greater risk of other cardiovascular disease [135,139], with a U-shaped risk

profile [135,136,140]. Other data suggest that only long sleep duration is associated with cardiovascular disease risk [141].

6.2. Immunity and Inflammation

Disturbances of sleep, as well as extremes of sleep duration, influence the risk of infectious and inflammatory disease and contribute to all-cause mortality [122,134,142,143]; this is a major public health concern given that approximately 25% of the population of the United States report insomnia complaints [144], and nearly 10% fulfill diagnostic criteria for chronic insomnia [145–147]. Sleep health [148] affects the immune system, with implications for infectious and inflammatory disease risk. Whereas sleep restores the immune system, sleep disturbance impacts adaptive and innate immunity, and plays a role in the risk of infectious disease and inflammation-related disorders including cardiovascular disease, cancer, and major depression [106].

Nocturnal sleep acts to ready the immune system for infectious challenge and to induce nocturnal activation of inflammatory signaling, and thus in the absence of sleep, nocturnal levels of inflammatory cytokines are lower during the night [149,150]. Concomitantly, loss of sleep induces an activation of sympathetic outflow, and the adrenergic signaling is thought to affect inflammatory gene expression and lead to increases in daytime levels of markers of innate immunity and inflammation [106].

Partial-night sleep deprivation, when repeated for several nights induces large increases in C-reactive protein (CRP) [151] and IL-6 [152]. Even shorter periods of sleep restriction induce increases in plasma concentrations of IL-6 in men and women, increases of TNF- α in men only [153], and increases in inflammatory transcripts of IL-1 β , IL-6, and IL-17 [154], with evidence that such increases persist even after a night of recovery sleep [154]. When sleep restriction or sleep fragmentation is limited to only one or two nights [155–157], or when sleep restriction occurs in the midst of intervening daytime naps [158,159], circulating levels of inflammatory markers do not appear to significantly change. However in those with underlying chronic sleep disturbances, a single night of sleep loss triggers the release of inflammatory markers such as IL-6 and TNF- α [160]. Sleep loss also results in a functional reduction of natural killer (NK) cellular activity in response to IL-2 activation [161,162]. Naps appear to be protective, as increases of IL-6 following four nights of sleep restriction are reversed by a 2-hour nap [163], and recent work demonstrates a reversal in salivary IL-6 and urinary norepinephrine increases in subjects who had the opportunity to take naps following a sleep deprived night [164].

6.3. Metabolic/Endocrine Function

A growing number of studies linking short sleep duration with increases in hunger and appetite, decreased glucose tolerance, increased risk of weight gain [165,166], and type 2 diabetes mellitus (T2DM) [167] have emerged in the last decade [168]. In one large study of Chinese patients with T2DM, the data suggested that poor sleep is prevalent in those with T2DM and inversely associated with quality of life [169]. In another study, short sleep duration in young, healthy men was associated with decreased leptin levels, increased ghrelin levels, and increased hunger and appetite [170]. A prior study [171] demonstrated that glucose tolerance was lower in those suffering with sleep debt, as were thyrotropin concentrations; additionally, evening cortisol concentrations and sympathetic

nervous system activity were increased in response to sleep deprivation. Sleep debt, it seems, confers a harmful impact on carbohydrate metabolism and endocrine function, similar to effects seen in normal ageing, arguing for the possibility that sleep debt may accelerate age-related chronic disorders [171].

6.4. Carcinogenesis

Shift work and related circadian disruption can result in a modification of circadian genes; these circadian genes serve as transcriptional regulators affecting the expression of many cancer-related genes and play a role in the regulation of cell division and DNA repair [106]. In long term shift and night workers, there has been found an increased risk for breast, prostate, colon, and endometrial epithelial malignancies as well as non-Hodgkin's lymphoma [172–175]. Whereas other studies failed to demonstrate an association [176], it has been concluded that there exists adequate evidence in humans to denote long-term shift work as a probable carcinogen, possibly related to a disruption in sleep homeostasis and melatonin secretion [177].

As with cardiovascular disease, no prospective study has examined whether sleep disruption elevates inflammation to mediate the relationships between sleep and cancer [106]; however, cancer risk may be increased by short sleep duration alone as demonstrated in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. In this study, those who reported a sleep duration of < 6 h had a significantly increased risk of cancer as compared with those who reported 7 h of sleep [178]. Other studies also suggested that extremes of sleep duration are associated with cancer risk [106]. Both short sleep (< 5 h) and long sleep (> 9 h) were associated with an increased risk of colorectal cancer in the 11-year follow-up of the Women's Health Initiative, as compared with those who sleep 7 h per night [179]. Another large-scale prospective study demonstrated that only long sleep duration (> 9 h) was associated with colorectal cancer risk, which was relatively more profound in men [180].

6.5. Athletic Performance

Being able to cope with physiological and psychological stressors is critical to athletic performance [181], and is affected by numerous factors including the natural fluctuation of physiological and behavioral processes across a 24-h period, such as the sleep–wake cycle, body temperature, and hormone regulation [182]. Currently, evidence delineating the importance of sleep for athletic performance or the effects of sleep loss on exercise performance is limited [183]. Preliminary data points to the possibility that athletes who are functionally over-reached present with sleep disturbances during high-volume training [184]. Prolonged bouts of strenuous exercise cause a temporary depression of various aspects of immune function, usually lasting approximately 3–24 h after exercise which may compromise resistance to common minor illnesses, such as upper respiratory tract infections and sleep disruption [185]. A decline in neurocognitive and physiological performance [1,186,187] is known to follow sleep loss, and since sleep disruption prior to significant sporting events is often reported in elite athletes [188–190], their performance might be compromised [188,191]. Current efforts to better understand the relationship between sleep and recovery are underway to help delineate the optimal sleep recommended for elite athletes.

7. Conclusion

In summary, this review points to the absolute necessity of sleep, albeit with a limited scientific understanding as to why. It is well-known that short and long sleep durations are related to greater prevalence and incidence of comorbidities, including T2DM [167], stroke [192], cardiovascular disease [136,193], obesity [194], carcinogenesis as well as mortality [195], indicating a likely optimal sleep duration recommended for adults of 7-8 hours [196].

Future research examining the proposed theoretical models of the reason for sleep, and the associations between sleep duration and the wide range of neurologic, cardiovascular, immune/inflammatory, metabolic/endocrine, and carcinogenic factors is needed. Prospective cohort studies measuring objective and self-reported sleep, sleep-related consequences, and sleep-related behaviors at each assessment period in concert with the incidence of various chronic illnesses should also be employed [197]. Ensuring the proper amount of sleep and offering ways to improve sleep quality is of paramount importance for disease prevention and health promotion in the population.

Conflict of Interest

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

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