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Sleep and energy balance: interactive homeostatic systems

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Abstract

For early humans, acquisition of food by hunting and/or gathering was a hunger-driven process requiring vigilance and (often) strenuous physical effort during daylight hours. To sustain such activities, hunter-gatherers also needed periodic rest and sleep—pursuits most effectively undertaken at night. In recent years, research has given us new insights into the physiologic underpinnings of these behaviors. Specifically, evidence has been uncovered indicating that the homeostatic regulation of food intake on the one hand and that of sleep on the other hand, are intertwined. Thus, carefully performed studies of eating behavior in rats indicate that duration of sleep after ingestion of a meal is closely correlated to the meal's energy content. In 1999, it was discovered that mice and dogs functionally deficient in the appetite-stimulating hormone, hypocretin-1, become narcoleptic, suggesting the existence of a "hard-wired" connection between regulation of hunger and satiety and regulation of sleep. Administered into the nucleus accumbens shell, hypocretin-1 induces feeding and locomotor activity in Sprague-Dawley rats. Hypocretin neurons in the hypothalamus are responsive to metabolic cues capable of signaling nutritional status. The suprachiasmatic nucleus, the body's principal circadian clock, exchanges information with the hypocretin system about the light/dark cycle and the body's metabolic condition. Circadian Clock mutant mice exhibit an attenuated diurnal feeding rhythm and become hyperphagic and obese. Both disruption of the circadian cycle and sleep deprivation can affect energy balance and, over time, may bring about substantial changes in body composition. Although there is growing evidence that interleukin-6 and several other proinflammatory cytokines are "sleep factors" that also affect energy balance, any possible role they might have in coordinating sleep/wakefulness with food-motivated behavior awaits clarification. Yet, the evidence is increasingly strong that the neurophysiologic and metabolic mechanisms responsible for the control of food-seeking behavior and the control of sleep and wakefulness are coordinated so that hunger and vigilance are paired during the daylight hours, and satiety and sleep are paired during darkness. The hypothalamic neuronal system that links these mechanisms is predominantly, but not exclusively, hypocretinergic, and is responsive to the suprachiasmatic nucleus circadian pacemaker and to certain metabolic signals of depletion and repletion.

1. Introduction

In the introductory paragraphs that follow, categorical statements are made about the relationship between food-seeking activity and the periodic need for rest and sleep in early humans (chosen as a model to avoid the confounding effects of civilization). These assertions are, for the most part, familiar and unremarkable. What has changed, however, is knowledge of the physiologic underpinnings of these behaviors. Recent research—some of which is summarized in this review—has provided new insights into the regulation of sleep and wakefulness and how this regulation might relate to energy homeostasis and the control of hunger and satiety.

Early humans, in order to survive, needed to obtain food—most often by some form of hunting and/or gathering. Many of the sources of food sufficient to meet their energy needs must have required considerable physical exertion. To remain in energy equilibrium, the hunters/gatherers needed food in quantities sufficient to offset their resting metabolic requirement, "everyday" physical activity, and the extra energy cost of the physical activity imposed by food seeking. The amount and duration of exertion that the human body can endure without becoming severely fatigued is strictly limited; therefore, industrious food seekers had to rest periodically to permit restoration of their capacity for physical work.

Because *Homo sapiens* evolved in a world that was alternately light and dark, elements of human physiology

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became entrained to this cycle and it was natural for humans to sleep at night and be active during the day. In addition to keeping early humans from remaining active at inappropriate times (hunting and gathering were not efficient during darkness), sleep conserved energy and—in modern parlance—was needed to "protect brain cells from the damaging effect of reactive oxygen species (ROS), allow sufficient time for the repair or replacement of essential cellular components in neurons and neuroglia, and deal with other biochemical consequences of waking metabolic activity" [1]. (Mammalian hibernation and the "torpor" exhibited by the Siberian hamster represent extreme examples of the adaptive use of sleep to conserve energy. Freeman et al [2] have reported that a suitable reduction in photoperiod can induce a winterlike phenotype in Siberian hamsters that " . . . includes a progressive decrease in food intake [functional satiety] . . . as well as reversible hypothermia in the form of short-duration torpor. Torpor [like hibernation] substantially reduces energy utilization . . .")

In early humans, prolonged sleep deprivation, for any of a number of reasons, would have wasted energy and interfered with the alertness and physical performance capability needed for acquisition of an adequate supply of food.

While an individual remains hungry, he or she is, for a time, more likely to be active and alert for opportunities to get food. Alleviation of hunger is a very high biological priority. After food consumption, the body is primed to rest and, if conditions permit, to sleep. Feelings of physical fatigue tell the body it is time to rest. The feeling of being "tired" is ordinarily a signal that the body needs sleep. However, it cannot be assumed that rest and sleep are parts of one physiologic continuum. As Rechtschaffen [3] puts it, "The frequent failure to distinguish between feelings of physical fatigue and feelings of sleepiness contributes to the widespread idea that sleep is for rest."

The longer an individual remains awake, the more urgent the need to sleep becomes. Eventually, sleep deprivation generates a severe dysphoria and the pressure to sleep becomes irresistible. Because the amount of sleep required by the body is regulated, its deprivation requires compensatory rebound sleep. After a period of satisfactory sleep, the individual awakens feeling refreshed and ready to resume food seeking.

In the following sections, recent investigations that have helped uncover parts of the neurophysiologic substratum of the behavioral scenario described above are briefly reviewed. Among the many neurologically based activities and "centers" implicated in sleep and energy balance, I have chosen to deal with 2 sets of paired behaviors: vigilance and food seeking on the one hand, and food ingestion and sleep on the other hand. Major modulators of these behaviors include nutritional status and the circadian pacemaker, together with certain relevant peptides. In the present review, attention is focused on the contributory roles of the suprachiasmatic nucleus, the hypocretins, and the cytokines.

2. Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) of the hypothalamus is the site of the dominant mammalian circadian clock. In this role, the SCN, which is entrained principally to the light-dark cycle, coordinates a number of circadian cycles within the mammalian organism, including the sleep-wakefulness cycle [4]. Taken in aggregate, the behavioral and neurobiologic evidence suggests that in rodents and humans, the circadian clock actively promotes both wake and sleep at different phases of the circadian cycle [5].

According to Kovacikova et al [6], "The molecular mechanism underlying generation of circadian rhythmicity within the SCN is based on interactive negative and positive feedback loops that drive the rhythmic transcription of clock genes and translation of their protein products." Photoperiod (the period of daily illumination that an organism receives) modulates phase, waveform, and amplitude of the rhythmic clock genes' expression (see Hamet and Tremblay, this issue, for a more detailed description).

The SCN is the recipient of dense retinohypothalamic innervation and can be said to function as part of the larger visual system [7]. In addition, the retinorecipient intergeniculate leaflet provides a major input to the SCN and its targets. The input to the SCN arises from the main pathway of the visual system in parallel to the optohypothalamic accessory input. Another major SCN afferent projection, which may serve as an inhibitory modulator of the effects of light on the circadian pacemaker, arises from the median raphe nucleus.

The SCN, in turn, provides inputs to the hypocretin-producing neurons in the hypothalamus—inputs that are mainly relayed via the subparaventricular zone and the dorsomedial nucleus [8]. These innervations are important because (as discussed earlier), the hypocretin-producing neurons target many wake-promoting regions. Yoshida et al [8] suggest that hypocretin neurons "may integrate a variety of interoceptive and homeostatic signals to increase behavioral arousal in response to hunger, stress, circadian signals, and autonomic challenges." In this context, it is noteworthy that homozygous Clock mutant mice are hyperphagic and obese. Unlike normal mice, which are mainly night eaters, Clock mutant mice " . . . have a greatly attenuated diurnal feeding rhythm . . . and develop a metabolic syndrome of hyperleptinemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia" [9]. Turek et al [9] also found that the expression of transcripts encoding certain hypothalamic peptides associated with energy homeostasis was attenuated in these mice—evidence suggesting that the circadian Clock gene network plays a significant role in mammalian energy balance.

The ventromedial arcuate nucleus (ARC) and the subependymal layer of the median eminence also have been shown to have reciprocal interaction with the SCN [10]. The ARC is recognized to be an integrator of long- and short-term hunger and satiety signals. Indeed, the ventromedial ARC

mainly comprises hypocretinergic neuropeptide agouti-related and neuropeptide Y neurons that are sensitive to circulating metabolic signals. Yi et al [10] have reported neuronal tracer and functionality studies indicating that the ventromedial ARC communicates peripheral metabolic information to the SCN—a finding that provides additional evidence for a reciprocal interaction between systems concerned with sleep and wakefulness and systems concerned with energy balance.

3. The hypocretins

In 1998, a hormone, named *hypocretin*, was discovered that, when injected in the cerebral ventricles, was observed to stimulate appetite in mice [11]. The same neuropeptide (also known as *orexin*) was found to have neuroexcitatory activity when added to a tissue culture of hypothalamic neurons [12]. Subsequently, it was reported that canine narcolepsy is caused by a mutation in the hypocretin receptor 2 gene [13]. At about the same time, Chemelli et al [14] reported that mice made hypocretin deficient by genetic alteration developed narcolepsy. These remarkable observations opened the door to a vastly improved understanding of the mechanism of human narcolepsy and, at the same time, provided new evidence for a physiologic link between food-motivated behavior and the regulation of sleep. Since 1998, hypocretin research has burgeoned.

The hypocretins are synthesized mainly by neurons situated in the posterolateral hypothalamus [15-17]. Hypocretin-1 is a 33-amino-acid peptide with an N-terminal pyroglutamyl residue and 2 intrachain disulfide bonds. Hypocretin-2 is a linear peptide of 28 amino acids. These neuropeptides act as potent agonists at the hypocretin-1 and -2 G-protein–coupled receptors, which show different distributions in the brain and differential affinities to the 2 hypocretins [17]. Hypocretin-1 neurons project to major arousal areas where they stimulate arousal while antagonizing sleep and muscle atonia [18].

Zhang et al [19] assessed the relative contribution of circadian and homeostatic factors on rate of hypocretin release. The problem was approached by studying the effect of surgically created lesions of the SCN on serially measured hypocretin concentrations in the cerebrospinal fluid (CSF). They found that control animals exhibited robust circadian and diurnal fluctuations in CSF hypocretin-1, locomotor activity, and core temperature. Peak CSF hypocretin-1 occurred at the end of the active period. In contrast, activity, temperature, and CSF hypocretin-1 were arrhythmic in the SCN-ablated animals. Significant correlations were observed between hypocretin-1 and physical activity both across and within animals, suggesting that interindividual and time-of-day differences in activity have significant effects on hypocretin release in SCN-lesioned animals. These findings indicate that hypocretin-1 release is under SCN control; however, locomotor activity also influences the activity of hypocretin neurons.

The neurotoxin, hypocretin-2-saporin, produces lesions in hypocretin receptor-bearing neurons. Gerashchenko et al [20] injected this compound bilaterally into the ventral tegmental area and substantia nigra (SN) of laboratory rats. The animals so treated developed insomnia and exhibited an increase in locomotion and hyperactivity. The authors speculated that insomnia after hypocretin-2-sap lesions of the SN could be secondary to the increased motor activity that results from reduction of tonic inhibitory control by the SN.

When infused into the lateral ventricles of awake animals, hypocretin-1 produces an increased duration of wakefulness compared with the response in vehicle-treated animals. Infused into the lateral ventricles of sleeping rats, hypocretin-1 produces substantial decreases in slow wave and rapid eye movement sleep. When hypocretin-2 is similarly injected, it has a weaker effect on these dependent variables than hypocretin-1 [21].

Electrophysiologic studies have shown that hypocretin neurons are responsive to monoamines and acetylcholine, and also metabolic cues, including leptin, glucose, and ghrelin [22]. Cholecystokinin octapeptide (CCK-8S) activates hypocretin neurons through the cholecystokinin A receptor [23]. Hypocretin neurons are also activated by neurotensin, oxytocin, and vasopressin and have functional interactions with hypothalamic feeding systems and monoaminergic/cholinergic centers [22]. According to Sakurai [22], “hypocretin neurons provide a critical link between peripheral energy balance and the central mechanisms that coordinate sleep/wakefulness and motivated behavior, such as food seeking.”

Thorpe [24] has demonstrated that hypocretin receptors and varicosities exist within the nucleus accumbens shell. Administration of hypocretin-1 via guide cannulae directed to the medial portion of the nucleus accumbens shell induced feeding and locomotor activity in Sprague-Dawley rats. These findings support the hypothesis that the nucleus accumbens is a site for hypocretin-1 modulation of feeding behavior and locomotor activity. Hypocretin-1 also stimulates gastric emptying of a nutrient liquid and gastric acid secretion independently of gastrin. This observation suggests a role for endogenous hypocretin in the preabsorptive processing of nutrients in the gut [25].

Taheri et al [26] have suggested that sleep duration may be an important regulator of body weight and metabolism. An association between short habitual sleep time and an increased body mass index (BMI) has been found in large population samples. In a group of 1024 volunteers from the Wisconsin Sleep Cohort Study, persons who habitually experienced short sleep duration typically displayed reduced leptin and elevated ghrelin levels. This hormonal pattern would be expected to increase appetite, providing a possible explanation for the increased prevalence of overweight associated with short sleep duration. Among persons sleeping less than 8 hours per night (74.4% of the sample), BMI was inversely proportion to duration of sleep—the

shorter the sleep duration the greater the BMI. Unfortunately, hypocretin values in the short sleepers were not reported. In the authors' words, "In Western societies, where chronic sleep restriction is common and food is widely available, changes in appetite regulatory hormones with sleep curtailment may contribute to obesity."

4. Cytokines

The subjective experience we call "sleepiness" or "tiredness" can range from mild to extreme. The severity of the experience—in terms of degree of dysphoria—depends in considerable part on the size of an individual's sleep deficit at the time and on the amount of physical energy expended by that individual in the recent past. Feelings of tiredness or exhaustion could be termed "behavioral sensations" (sensations giving rise to behaviors designed to restore homeostasis).

Cytokines are important signaling molecules of the peripheral immune system that may regulate/modulate sleep during health [27]. Vgontzas et al [28] have suggested that in the presence of a high cortisol concentration, the proinflammatory cytokine, interleukin-6 (IL-6), contributes to feelings of tiredness and fatigue. Indeed, these authors consider IL-6 to be a likely "sleep factor" because (*a*) its circadian secretion correlates with sleep/sleepiness; (*b*) after experimentally induced sleep deprivation, IL-6 peaks during the day in contrast to its pattern of secretion in healthy young adults; (*c*) it is elevated in disorders that generate excessive daytime sleepiness such as narcolepsy and obstructive sleep apnea; (*d*) it is somnogenic in rats and exhibits a diurnal rhythm that tracks the sleep/wake cycle in these animals. Burgos et al [29] have reported that nocturnal IL-6 was increased in patients with impaired sleep documented by polysomnographic studies. In the insomniac patients, total IL-6 secretion showed an inverse correlation with subjectively perceived sleep quality and amount of slow wave sleep. Therefore, in a sense, circulating concentrations of IL-6 can be thought of as reflecting the "sleep debt" that accumulates as a consequence of sleep deprivation.

The foregoing studies suggest that an increase in the circulating levels of IL-6 may signal tiredness and fatigue and may contribute to the dysphoria associated with sleep deprivation. However, as presented, the evidence also suggests that when IL-6 levels are elevated, this cytokine does not inevitably generate sleep inasmuch as it is said to contribute to *poor* sleep when the stress system is activated (high cortisol); moreover, its secretion is increased *during* periods of insomnia. Cytokines may either promote or inhibit sleep according to Kapsimalis et al [30]. These authors suggest that IL-1 and tumor necrosis factor also play a role in regulation of non–rapid eye movement sleep. The hypothalamic preoptic area and the basal forebrain are sites of action for such regulation, which includes direct receptor-mediated effects on neurons. There appears to be an appreciable overlap between the circadian pacemaker, the cytokine systems, and other neurohumoral systems (including the hypocretin system and the hypothalamic-pituitary-adrenal axis) with respect to their influence on sleep-wake regulation.

During illness, cytokines appear to "orchestrate" the body's response to infection and other pathogenetic processes. Opp [27] has stated that in sick persons, the brain "detects activation of the peripheral immune system and responds by altering physiological processes and complex behavior, including sleep. These changes [including the restorative effect of sleep] function to support the immune system and restore health." On the other hand, cytokine excess, also known to cause anorexia, has been reported to play a major role in the pathophysiology of cachexia [31].

Population surveys have shown elevated IL-6 levels to be risk factors for cognitive impairment, the metabolic syndrome, hypertension, diabetes, carotid artery atherosclerosis, and heart disease [32]. The conditions under which IL-6 serves a useful physiologic purpose and under which it may become seriously detrimental to health and longevity await clarification.

5. Discussion

In the foregoing pages, an attempt has been made to identify possible neurophysiologic determinants of some of early humans' putative periodic behaviors, such as hunger-driven pursuit of food during the day and its consumption, followed by satiation, rest, and sleep, principally at night. The existence of a connection between food consumption and subsequent sleep has been noted and commented on anecdotally for many years. In 1825 (the year before his death), the legendary French gastronome, Brillat-Savarin [33], affirmed (in translation): "A hungry man cannot sleep; the cravings of his stomach keep him painfully awake.... He, on the contrary, that has exceeded the bounds of discretion in his eating, falls asleep immediately...."

The relationship between food ingestion and sleep has been observed in laboratory rats in which the "complete behavioral sequence of satiety" was reported to culminate in a state of sleep after meal ingestion [34]. Yet, the actual physiologic basis for the association between ingestion of food and sleep was not systematically investigated until the late 1970s, when Nicolaidis and associates [35,36], using precise measurements of feeding and sleeping behaviors in normal rats, found a high correlation between the energy size of a meal and the duration of sleep during the interval after the meal. A similar relationship between meal size and subsequent sleep pattern was also observed in rats receiving hypothalamic lesions that made them either hyperphagic or aphagic/hypophagic. Further experiments suggested that the relationship between meal size and amount of subsequent sleep could be attributed to the effect of feeding on the "background" metabolic rate, namely, the fraction of total metabolism that remains after the metabolic cost of physical activity has been factored out of the calculation [37]. (See Nicolaidis, this issue, for further details.)

The discovery in 1999 that mice [14] and dogs [13] functionally deficient in the appetite-stimulating hormone, hypocretin-1, become narcoleptic, immediately suggested the existence of a "hard-wired" connection between regulation of appetite for food and regulation of sleep. Subsequent studies have supplied additional evidence for an important role of hypocretin neurons in linking sleep and energy balance. For example, when administered directly into the medial nucleus accumbens shell, hypocretin has been found to induce feeding and locomotor activity in Sprague-Dawley rats [21]. Inasmuch as lack of hypocretin is associated with narcolepsy, this finding is consistent with the notion that an increase in the activity of the hypocretin system promotes vigilance together with feelings of hunger and behaviors, such as locomotion, that are geared to food seeking.

Hypocretin neurons have also been shown to be responsive to metabolic cues such as leptin, glucose, ghrelin, and cholecystokinin octapeptide [22]. Moreover, hypocretin-1 stimulates gastric emptying of a nutrient liquid, suggesting a role in the preabsorptive processing of nutrients in the gut [25]. Thus, there appears to be a two-way communication between the mechanism that regulates sleep and the mechanism that regulates energy balance.

There is also a clear relationship between the circadian clock (the SCN), the hypocretin system, and other systems concerned with energy balance. The SCN provides inputs to hypocretin-producing neurons in the hypothalamus [8] and receives metabolic information from the ventromedial ARC, which, in turn, is responsive to a variety of metabolic signals [10]. Normal rats exhibit robust circadian and diurnal fluctuations of CSF hypocretin-1; however, physical activity, temperature, and CSF hyopocretin-1 become arrhythmic in SCN-ablated animals [19]. Interestingly, Clock mutant mice become hyperphagic and obese, and (in contrast to normal mice that eat mainly at night) exhibit a "greatly attenuated" diurnal feeding rhythm [9].

Among more than 1000 participants in the Wisconsin Sleep Cohort Study, persons whose sleep was habitually of short duration exhibited reduced leptin and elevated ghrelin concentrations—a hormonal pattern consistent with appetite stimulation [26]. In this cohort, BMI (in kilograms per meter squared) varied inversely with sleep duration among those who slept less than 8 hours per night.

Whereas certain proinflammatory cytokines (notably IL-6) are thought by some investigators to be sleep factors [28], they also affect energy balance indirectly by contributing to feelings of sleepiness or, in the case of illness, by creating sufficient dysphoria to cause the animal or human to remain inactive, thereby supporting the body's efforts to deal with an infection or some other pathogenic process [27]. Cytokine excess is also thought to be a major cause of illness-associated cachexia [31].

In conclusion, the evidence is increasingly strong that the neurophysiologic and metabolic mechanisms responsible for the control of food-seeking behavior on the one hand, and sleep and wakefulness on the other, are coordinated, so that, operationally, hunger and vigilance are paired during the daylight hours and satiety and sleep are paired during darkness. The hypothalamic neuronal system that links these mechanisms is predominantly hypocretinergic and is responsive to the SCN circadian pacemaker and to certain metabolic signals of depletion and repletion.

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