Neural Circuitry Responsible for Sleep and Wakefulness

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Abstract

Research over the past 50 years has determined that specific neurons in the brain are responsible for generating waking, non-REM sleep, and REM sleep. Some of the neurons responsible for keeping us awake are also involved in regulating energy metabolism. One such arousal neuronal population contains the neuropeptide hypocretin, also known as orexin. The HCRT neurons are located in the hypothalamus, an area that also contains other neurons regulating energy metabolism. The hypocretin neurons are most active during waking and silent during sleep, and their activity has been shown to regulate brown adipose tissue (BAT) thermogenesis. The hypocretin neurons are also activated by low glucose levels and shut off when the glucose levels increase. Thus, the activity of the hypocretin neurons is linked to energy metabolism. Based on this relationship, it is easy to see how inadequate sleep or even frequent arousals during sleep, as occurs in obstructive sleep apnea, will affect energy metabolism and adiposity.

Introduction

It was initially hypothesized that sleep was a passive process resulting from lack of sensory stimulation to the brain. This hypothesis was rejected when rapid eye movement sleep (REM sleep) was discovered [1, 2], and it was found that during REM sleep the brain was as active as in waking. With that discovery, it became clear that in humans there was a process in the brain that periodically "awakened" the sleeping brain every 90 min at night. We now know that specific neurons are responsible for generating wake, non-REM, and REM sleep (Fig. 3.1). There is a tight link between arousal and feeding, and peripheral signals such as glucose activate arousal neurons, so that the animal can forage for food. Indeed, some of the sleep and arousal neurons reside in areas that regulate feeding. In this chapter, we review the evidence linking arousal, feeding, and sleep.

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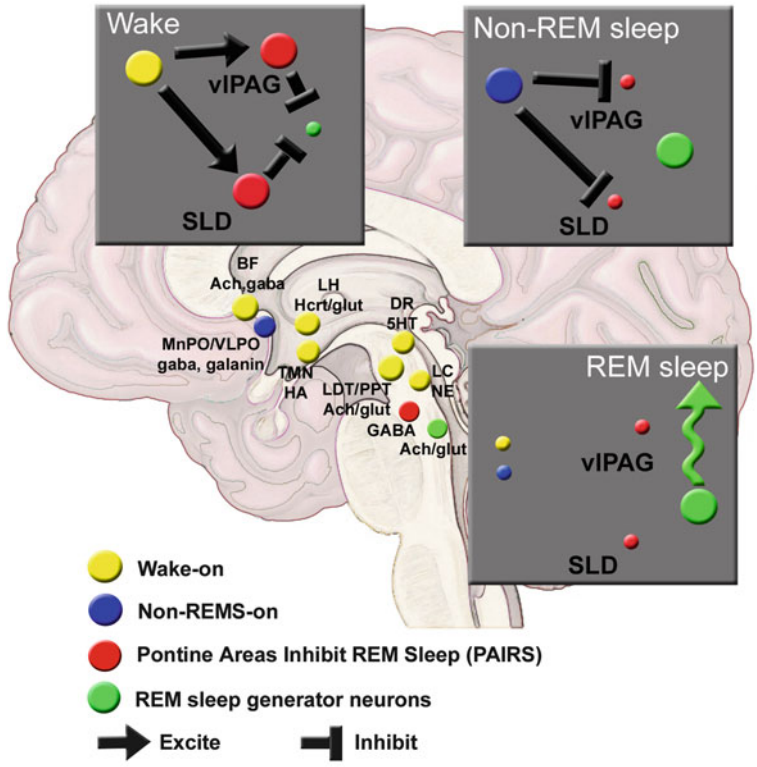

Fig. 3.1 A coordinated interaction between neuronal populations is responsible for wake, non-REM sleep, and REM sleep. Neuronal populations that are considered to generate wakefulness (*yellow*) interact with neurons that generate non-REM sleep (*blue*). Both act on neurons in the pontine brainstem (*red*) and influence the generation of rapid-eye movement sleep (REM sleep). Wake-on neurons inhibit REM sleep by activating pontine GABA neurons in the pons. The strength of the excitatory input to the pontine GABA neurons (*red*) influences REM sleep. A strong input will inhibit REM sleep while a weakened input will facilitate it. This excitatory input to the GABA pontine neurons is from hypocretin and from other sources. The purpose of this excitation is to keep the animal upright and mobile while foraging for food. During non-REM sleep the excitatory input to the pontine GABA neurons is lost and is replaced by a strong inhibitory input. This enables REM sleep generator neurons (*green*) to become active and when sufficient numbers of these are activated then REM sleep ensues. The hypothesis that the pontine areas inhibit REM sleep has been tested in two separate studies from our lab [3–5]. The earlier study tested the hypothesis in rats whereas the second study tested it in mice. In both studies REM sleep increased when the GABA neurons were lesioned with hypocretin-2 saporin thereby supporting the hypothesis of PAIRS. *Ach* acetylcholine, *BF* basal forebrain, *DR* dorsal raphe, *GABA* gamma amino butyric acid, *GLUT* glutamic acid, *HA* histamine, *HCRT* hypocretin, *LC* locus coeruleus, *LH* lateral hypothalamus, *MnPO* median preoptic nucleus, *NE* norepinephrine, *LDT* lateral dorsal pontine tegmentum, *PPT* pedunculopontine tegmentum, *SLD* sub lateral dorsal nucleus, *TMN* tuberomammillary nucleus, *vlPAG* ventral lateral periaquaductal gray, *VLPO* ventral lateral preoptic nucleus. Reprinted with permission from [5]

Neurons Responsible for Sleep

The Ventral Lateral Preoptic Area

This is a small region located in the preoptic area comprising primarily of neurons containing GABA and galanin. These neurons project to and are inhibitory to all of the arousal neurons [6]. The ventral lateral preoptic area (VLPO) neurons are inhibited by the wake-active neurotransmitters, acetylcholine, serotonin, and norepinephrine, but are unaffected by histamine [7]. The VLPO neurons were identified using the immediate-early gene c-FOS [8]. Subsequently, a region dorsal to the VLPO, the median

preoptic area (MPO) was identified as sleep active based also on c-FOS immunohistochemistry. Electrophysiology studies have now more definitively determined that VLPO/MPO neurons begin to fire during drowsiness and peak activity is seen during non-REM sleep. The sleep active cells comprise about 25% of the recorded cells in the basal forebrain-preoptic area and are intermixed with wake-active cells which predominate. Electrical stimulation or warming of the VLPO/MPO area induces sleep. Lesions of the VLPO decrease sleep and increase wake [9]. The VLPO and MPO neurons are now linked to sleep pressure [10, 11] and turn on when the wake-active neurons stop firing. Optogenetic methods are currently being used to drive these neurons to initiate sleep. VLPO/MPO neurons project to the pontine regions responsible for gating REM sleep [12].

Recently, sleep-active neurons were identified in the cortex and found to contain GABA, neuronal nitric oxide synthase (nNOS), and some also contained neuropeptide Y [13]. These neurons were diffusely scattered in all cortical layers in the rat, but in the mouse they were predominantly in layers V and VI. Activation of these neurons during sleep would inhibit cortical neurons, while nNOS may dictate sleep pressure since the intensity of sleep was found to be directly related to the number of nNOS expressing GABAergic cortical neurons [13].

Melanin Concentrating Hormone

Neurons containing the neuropeptide melanin-concentrating hormone (MCH) are located primarily in the posterior hypothalamus. These neurons are separate and distinct from the hypocretin neurons, but located in the same region as the hypocretin neurons. They also project to many of the same regions in the brain as the hypocretin neurons. MCH exerts its action via two metabotropic receptors, the MCHR1 and MCHR2, but only the MCHR1 is present in rodents. MCH neurons are active primarily during sleep, especially during REM sleep, and MCH knockout mice have less REM sleep. Intraventricular microinjection of MCH increases both slow wave sleep (SWS) and REM sleep. This evidence suggests an important role of this peptide in sleep.

There is very strong evidence that MCH increases food intake and reduces energy expenditure [14, 15]. For instance, acute infusion of MCH into the lateral ventricles induces feeding in rodents [16]. Mice with deletion of the pre-pro-MCH gene [17] or of the MCH neuron (ataxin-MCH transgenic mice) are lean, hypophagic, and have increased energy expenditure [18]. Mice lacking MCH receptors are hypophagic and lean with increased metabolic rate. MCH-1 receptor antagonists produce significant weight loss in rodent models of obesity and do so by reducing meal size [19].

Neurons Responsible for Arousal

There are many more neuronal populations linked to arousal compared to sleep. The arousal neurons include not only the classical neurotransmitters but also the peptide, hypocretin. Research during the last decade leads us to conclude that one reason for the diverse population of arousal neurons is that some of these populations arouse a sleeping brain in response to specific situation. For instance, the histaminergic and noradrenergic neurons trigger arousal in the event of an alarm (either internal or external) and maintain vigilance in a stressful condition. The basal forebrain cholinergic neurons rapidly bring cognitive functions online when awakened from sleep. Lesions of all three of these neuronal populations do not change overall levels of wakefulness but when the histaminergic or the LC neurons are lesioned then it decreases arousal in unfamiliar conditions [20]. Previously, we reviewed the evidence linking the histamine, noradrenaline, and acetylcholine neurons to arousal [21].

It is also important to have neurons that respond to hunger, which then triggers the overall arousal network to allow foraging for food. A number of peptides and neurotransmitters are located within the hypothalamus, and their role in

sleep and wakefulness has been reviewed [22]. In this paper, we will specifically focus on neurons containing the neuropeptide hypocretin, which is located primarily in the posterior hypothalamus. The growing body of evidence, amassed only within the last 10 years, shows that these neurons are linked to sleep and wakefulness and also regulate energy metabolism.

Hypocretin

The peptide hypocretin, also known as orexin, was discovered by two independent groups using different approaches [23–25]. The hypocretins were linked to narcolepsy as a result of the discovery that canines with narcolepsy possess a mutation in the hypocretin-2 receptor [26]. This was then supported by the finding that mice with deletion of the hypocretin/orexin gene exhibit symptoms of narcolepsy [27]. Narcoleptic patients have a loss of the hypocretin-containing neurons [28, 29] and low CSF concentrations of HCRT-1 [30]. Narcoleptic patients, hypocretin knockout mice, and the hypocretin-2 receptor knockout mice weigh significantly more than age-matched controls [27, 31].

The hypocretin neurons project to sites involved in waking and REM sleep. The heaviest projections are to the locus coeruleus (LC) and the tuberomammillary nucleus (TMN). Hypocretin fibers also innervate the dorsal raphe and basal forebrain. Immunohistochemistry indicates that one or both of the receptor subtypes (hypocretin-1 and hypocretin-2 receptors) are expressed in the dorsal raphe, the lateral dorsal tegmental (LDT) nucleus, LC, the locus subcoeruleus, pontis oralis, Barrington's nucleus, the trigeminal complex (mesencephalic trigeminal and motor nucleus of the trigeminal nerve), the dorsal tegmental nucleus of Gudden, the ventral cochlear nucleus, trapezoid nucleus, pontine raphe nucleus, and the pontine reticular nucleus. Complementary analysis of hypocretin receptor mRNA with a cRNA probe shows that hypocretin receptor mRNA is also detected in areas that show protein immunoreactivity, suggesting the mRNA and protein are co-localized.

The receptor is present on neurons involved in mastication, bladder control, gastrointestinal function, and arousal. Given these projection sites and the functions associated with these sites, we hypothesize that hypocretin acts to keep the animal alert and vigilant while engaged in feeding behavior. Hypocretin has a powerful wake-promoting effect and receptor antagonists that block one or both receptors [32] cause sleepiness. In nonhuman primates, inhalation of hypocretin produces arousal even after sleep deprivation [25]. The activity of the HCRT neurons is consistent with promoting arousal. Identified HCRT neurons are active during wake and silent during sleep [33–35]. They begin to fire in anticipation of arousal, and they are easily activated during sleep [35].

Initially it was hypothesized that the hypocretin neurons regulate feeding. However, since then a number of studies, including our own [36] have found that food intake is not changed in hypocretin-KO mice or in mice lacking the hypocretin neurons [37–40]. Hypocretin neurons are sensitive to glucose, ghrelin, and leptin [41]. Hypocretin neurons are also sensitive to and activated by amino acids [42]. The inputs from the ventral medial hypothalamus and the lateral hypothalamus would arouse the animal because glucosensing neurons in these regions [43] respond to a very narrow range of glucose levels (0.1–2.5 mmol/l). A lower glucose level, which is likely at the end of a rodent's sleep period (during the day in nocturnal rodents), would activate arousal neurons so that the animal can forage for food and restore energy balance. Indeed, the HCRT neurons are activated by low glucose levels and shut off when the glucose levels increase [44]. Not surprisingly, hypocretin and MCH neurons respond in a different way to glucose [45]; high glucose inhibits hypocretin neurons but stimulates MCH neurons. In other words, the increased glucose decreases activity of the arousal promoting hypocretin neurons and increases activity of the sleep promoting MCH neurons. This makes perfect sense given that after a meal there is a high tendency to sleep whereas hunger promotes arousal.

SIRT-1, CLOCK, Energy Metabolism, and Hypocretin

As noted earlier, loss of hypocretin or of its receptor increases adiposity. Enhanced orexin receptor 2 signaling prevents obesity [46]. The weight gain may be the result of impaired brown adipose tissue (BAT) thermogenesis [47]. In the brain, orexin input to the raphe pallidus has been shown to regulate BAT thermogenesis [48]. Waking would drive sympathetic outflow resulting in increased energy expenditure and compensatory increase in feeding. Waking at an inappropriate time of day such as what occurs with shift work will also affect energy metabolism.

How might peripheral metabolic signals feedback onto arousal neurons? SIRT-1 may link energy metabolism to hypocretin. SIRT-1 is an enzyme that epigenetically regulates gene expression by using energy stored in nicotinamide adenosine dinucleotide (NAD+) to remove the acetyl group from histones. In so doing, SIRT-1 changes chromatin structure. Recently, it was discovered that SIRT-1 counteracts the activity of CLOCK [49, 50]. As reviewed elsewhere in this book (see Chaps. 1 and 2) CLOCK dimerizes with BMAL1 which then sets into motion an intracellular cascade that regulates circadian rhythms. However, CLOCK acetylates histones, and SIRT-1 associates with the CLOCK:BMAL1 heterodimer to deacetylate histones. SIRT-1 is exquisitely sensitive to glucose [51] and by coupling with CLOCK it may transduce peripheral metabolic signals to the circadian clock. This would then regulate the amplitude of the intracellular cascade underlying circadian rhythms.

SIRT-1 is increased when food is scarce and coordinates the increase in hepatic glucose production [52]. Food restriction also increases SIRT-1 in hypothalamic areas involved in energy metabolism [53]. They also showed that SIRT-1 upregulates the hypocretin-2 receptor. Putting this together, it would appear that reduction in glucose may cause arousal by activating the hypocretin neurons. The intracellular signal involving SIRT-1 upregulates the hypocretin-2 receptor, thereby strengthening the link between the hypocretin ligand and its receptor. This then enables the animal to have the proper locomotor ability to forage for food. Failure of this link, either through loss of the ligand or the hypocretin-2 receptor, causes inadvertent collapse of motor control as in narcolepsy.

Basal Forebrain and Acetylcholine

Acetylcholine was one of the first neurotransmitters linked to arousal. Acetylcholine is released in the cortex during waking and REM sleep [54–57]. The cholinergic neurons in the basal forebrain are the source of the acetylcholine release in the cortex because when these neurons are lesioned there is a decrease in cortical acetylcholine levels [58]. The release of acetylcholine is evident in the wake-active hemisphere even in mammals that display uni-hemispheric sleep [59].

Hypocretin neurons can drive the BF cholinergic neurons. A direct effect of hypocretin-1 on the BF cholinergic neurons has been shown [60]. Hypocretin depolarizes BF cholinergic neurons via the hypocretin type 2 receptor. Moreover, administration of hypocretin-1 into the BF via reverse microdialysis produces a dose-dependent increase in acetylcholine in the prefrontal cortex [61]. In that study, when the hypocretin-1 was applied to the prefrontal cortex no change in acetylcholine was observed indicating that the release was from the BF cholinergic neurons.

Infusion of hypocretin to the BF induces wakefulness [62, 63]. The wakefulness is produced even in rats with lesions of the cholinergic neurons in the BF indicating that hypocretin receptors on the noncholinergic neurons can drive wakefulness [64]. These wake-active noncholinergic neurons might be GABAergic innervating cortical GABA interneurons and may cause arousal through disinhibition [65].

The BF also contains sleep-active neurons, some of which contain neuropeptide Y [66]. These sleep-active neurons would be disinhibited when the wake-active BF neurons become silent [67]. The GABAergic neurons increase activity

in conjunction with cortical slow waves [68]. They project to the cortex [69] and to the posterior lateral hypothalamus where the hypocretin neurons are located. Their activity would suppress activity of the hypocretin wake-active neurons and promote sleep.

Hypocretin neurons are active only during wake [34], and we hypothesize that their activation would drive downstream targets such as the BF neurons, which release acetylcholine into the cortex and facilitate cognitive function. In our model, the BF is not regulating daily levels of waking as traditionally hypothesized, but instead its activation during waking is important for memory and cognitive functions. Thus, we hypothesize that one important function of the BF neurons is to rapidly mobilize cognitive function when one is awakened from sleep. In other words, it is important to be cognitively aware of one's surrounding upon awakening from sleep.

The Tuberomammillary Nucleus and Histamine

In the brain, histamine neurons are located exclusively in the TMN [70]. Histamine has a potent arousal effect, and antihistamines produce drowsiness and sedation. Histamine microinjections into projection sites such as the basal forebrain produce a dose-dependent increase in wake [71]. When histamine synthesis in the preoptic area is blocked, sleep increases and wakefulness decreases [71]. Histamine H1 and H2 receptors are postulated to mediate the arousal [71].

Since histamine produces arousal, it is reasonable that histamine neurons should be active during waking. Electrophysiology studies have found that histamine neurons in the TMN region have the highest discharge rate during waking and are virtually silent during sleep [72]. In narcoleptic canines, TMN neurons are also active only during waking and silent during sleep [73].

The hypocretin neurons innervate the TMN and the hypocretin-2 receptor is heavily expressed on these neurons [74]. Hypocretin stimulates identified histamine neurons [75]. However, there does not appear to be a reciprocal histamine/TMN projection to the hypocretin neurons [76], nor is there a direct effect of histamine on identified hypocretin neurons [77]. This suggests that histamine neurons in the TMN are driven by the hypocretin neurons. The histaminergic neurons would then activate the cortex directly via their widespread hypothalamo-cortical projections or, indirectly, by stimulating the basal forebrain cholinergic system. The net effect of the hypocretin-TMN stimulation would be to arouse the cortex.

The Locus Coeruleus and Norepinephrine

The LC contains primarily norepinephrine neurons that innervate virtually the entire brain and spinal cord. Electrophysiology studies have found that the noradrenergic LC neurons are most active during waking, less active during non-REM sleep, and they stop firing during REM sleep [78, 79]. The LC receives an especially heavy innervation of hypocretin fibers [80] but surprisingly, the LC does not project to the hypocretin neurons [76]. LC neurons contain primarily the hypocretin-1 receptor [81]. Hypocretin excites LC neurons and potently increases waking and decreases REM sleep [82, 83].

Serotonin (5-Hydroxytryptamine)

Serotonin neurons are localized in the raphe. These neurons are most active in waking, less active during non-REM sleep, and virtually silent during REM sleep [84]. Thus, these neurons behave very much like the orexin, histamine and LC neurons, in that they are all wake-active. Serotonin exerts its actions via seven distinct receptors (5-HT 1–7), which are G protein-coupled receptors, except 5-HT-3 which is a ligand-gated ion channel. Some of these receptors also have distinct subtypes. Through these receptors, serotonin can act as both an activator and an inhibitor.

Sleep has been examined in specific serotonin receptor knockout mice [85]. 5-HT1A and

5HT1B receptor knockout mice have more REM sleep compared to wild-type mice, and there is no REM sleep rebound after REM sleep deprivation [86, 87]. 5HT1A and 1B receptor agonists block REM sleep whereas the antagonists increase it. These effects are absent in the respective receptor knockouts. These effects can be explained because stimulation of the 5HT1A or 1B receptor hyperpolarizes the neuron and loss or antagonism of these receptors produces disinhibition of the REM sleep generator neurons. This was clearly demonstrated in a study that monitored the activity of individual REM sleep generator neurons in response to local pharmacological stimulation. It was found that administration of 8-OH-DPAT, a selective 5HT1A agonist via reverse microdialysis into the pontine region in rats decreased REM sleep by blocking the activity of REM sleep generator neurons in the pontine tegmentum [88]. This may also explain how selective serotonin reuptake inhibitors (SSRIs) decrease REM sleep.

5-HT2 receptor stimulation depolarizes neurons. 5-HT2A [89] or 2C [90] receptor knockouts are awake more and sleep less. 5-HT2A antagonists such as MDL100907 (0.1, 1.0, and 3.0 mg/kg IP) increase non-REM sleep and delta power without affecting REM sleep [91]. Ritanserine, a broad spectrum antagonist of the 5-HT2 receptor, also increases non-REM sleep [92] . 5HT6 receptor stimulation depolarizes neurons but the effects on non-REM sleep of the antagonist, RO4368554 have been mixed at the highest dose tested (10 mg/kg, IP). One study [91] found increased non-REM sleep at night whereas another study found no effect [93].

With respect to feeding, exogenous 5-HT or drugs that stimulate serotonin signaling decrease food intake while drugs that antagonize serotonin receptor signaling increase food intake. In this regard, D-fenfluramine and phenetermine, which release serotonin produce significant weight loss. These compounds were withdrawn following a number of cases of pulmonary hypertension and cardiac valvulopathy. Another compound that produces significant weight loss is sibutramine. It acts by increasing noradrenaline and serotonin levels in the hypothalamus, nucleus accumbens and the brainstem, all regions associated with energy homeostasis.

Specific serotonin receptors are being targeted for weight loss. For instance, administration of agonists specific to the 5-HT1A receptor increases feeding, whereas agonists specific for the 5-HT1B and 5-HT1C receptors decrease food intake. Selective stimulation of the 5-HT2C receptor decreases food intake and body weight in both lean and obese rodents. These agonists may exert their hypophagic actions via stimulation of receptors located on POMC containing neurons within the arcuate (ARC) nucleus. Mice lacking the 5-HT2C receptor are hyperphagic and weigh more. Selective reintroduction of 5-HT2C receptors on POMC containing neurons rescues the obese phenotype [94–96]. The 5-HT6 receptor is also a potential target for the treatment of obesity [97] since knockout mice do not gain weight when placed on a high-fat diet and the 5-HT6 receptor antagonist, RO 04-6790, significantly reduces weight [98].

Neurons Regulating REM Sleep

Converging data from a variety of studies indicates that REM sleep originates from the pons (summarized in [99]). Neurons that are selectively active during REM sleep and that are likely to generate REM sleep are present in the pons. Using c-FOS we have found that some of the cholinergic neurons in the LDT and pedunculopontine tegmental (PPT) nuclei of the pons are REM sleep-on neurons [100]. These REM sleep-on neurons are inhibited by GABA neurons located in regions of the pons that we refer to as pontine areas inhibiting REM sleep (PAIRS) [3]. One group of these GABAergic neurons resides in the sublateral dorsal tegmental area (just ventral to the LC) and an additional group resides in the ventral lateral periaqueductal gray (vlPAG).

HCRT and other wake-active neurons (such as the LC, serotonin, histamine) activate the pontine GABAergic neurons, which then block the REM sleep-on neurons [101]. If this is the case, then lesion of these pontine GABA neurons should increase REM sleep, which it does. For instance,

HCRT2-saporin-induced lesions of these neurons potently increase REM sleep in both rats [4] and mice [3]. During wake, these pontine GABAergic neurons would be activated and levels of GABA should be high in the pons, which is the case [102]. When the hypocretin neurons are silent, or destroyed as in narcolepsy, then the pontine GABA neurons do not fire effectively which then allows the REM-on neurons to become disinhibited. Mice and rats that lack hypocretin enter into REM sleep often (for review see [76]). Canines with a mutation of the hypocretin-2 receptor also have abnormal onset of REM sleep.

Night-Eating Syndrome

This is a syndrome occurring more often in obese individuals where the individual consumes most of their food from late in the evening into the early hours of the morning [103]. In 1955, Stunkard observed such an eating pattern in 64% of a group of very obese females and established criteria for night eating syndrome (NES) which included nocturnal hyperphagia, insomnia, and morning anorexia [104]. Recent evidence has indicated that patients with NES display a delayed circadian pattern of food intake but retain a normal sleep–wake cycle. A comparative study on the eating and sleep–wake patterns of persons with NES with those of matched control subjects found no difference between the total energy intake, but the pattern of energy intake was different [105]. Food intake after the evening meal, as a proportion of the 24-h intake was more than threefold greater in NES subjects than in controls. NES subjects had sleep onset, offset, and total sleep duration times comparable with those of controls. NES subjects had more nocturnal awakenings than did controls, and their actigraphically monitored arousals occurred earlier during sleep. NES subjects consumed food on 74% of the awakenings vs. 0% for the controls. This suggests a phase delay in energy consumption relative to sleep–wake times in NES.

Another study examined the phase and amplitude of behavioral and neuroendocrine circadian rhythms in patients with NES [106]. Fifteen women with NES (mean age ± SD, 40.8 ± 8.7 years) and 14 control subjects (38.6 ± 9.5 years) were studied in the laboratory for three nights with food intake measured daily. Blood also was collected for 25 h (every 2 h from 0800 to 2000 h, and then hourly from 2100 to 0900 h) and assayed for glucose, insulin, ghrelin, leptin, melatonin, cortisol, thyroid-stimulating hormone [TSH], and prolactin. Control subjects displayed normal phases and amplitudes for all circadian rhythms. In contrast, patients with NES showed a phase delay in the timing of meals, and delayed circadian rhythms for total caloric, fat, and carbohydrate intake. In addition, phase delays of 1.0–2.8 h were found in two food-regulatory rhythms—leptin and insulin—and in the circadian rhythm of melatonin (with a trend for a delay in the circadian rhythm of cortisol). In contrast, circulating levels of ghrelin, the primary hormone that stimulates food intake, were phase advanced by 5.2 h. The glucose rhythm showed an inverted circadian pattern. Patients with NES also showed reduced amplitudes in the circadian rhythms of food intake, cortisol, ghrelin, and insulin, but increased TSH amplitude. Thus, patients with NES demonstrated significant changes in the timing and amplitude of various behavioral and physiological circadian markers involved in energy metabolism [106, 107].

A neuroimaging study found elevated brain serotonin transporter binding in the midbrain of individuals with NES. Administration of SSRIs restored the circadian rhythm of both food intake and neuroendocrine function [108].

Hypocretin and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a disorder in which during sleep the upper airway collapses and airflow is interrupted, which then forces the individual to awaken and resume breathing. As a result of the cessation of breathing during sleep, the individual is not able to maintain long bouts of sleep and fails to enter into the deeper stages of sleep, i.e., stages 3 and 4. Obesity is a risk factor in that fatty deposits in the upper airway produce

a narrowing of the upper airway, which then leads to cessation of airflow during sleep. OSA among obese patients exceeds 30%, reaching as high as 50–98% in the morbidly obese population.

Obese patients have an increase in leptin levels [109, 110]. Although leptin is considered to be a satiety signal to stop eating, it is not clear why the increased leptin levels in obese individuals do not stop food intake. It has been suggested that hyperleptinemia may be an indicator of OSA [111]. Treatment of OSA with nasal CPAP (continuous positive airway pressure) does decrease levels of leptin [112].

Ghrelin stimulates appetite and ghrelin levels are higher in patients with OSA compared to BMI-matched (body matched index) control subjects [113]. Continuous positive airway pressure (CPAP) treatment of 2 days does significantly reduce ghrelin levels in OSA patients [114]. The appetite-stimulating effects of ghrelin may well contribute to increased caloric intake and weight gain in patients with OSA.

The elevated levels of both leptin and ghrelin in OSA suggests that in OSA the feedback regulatory process that controls food intake has been compromised. One possibility is that the increased sleep fragmentation in these patients produces a sleep loss, which increases energy metabolism. As a consequence, the individual eats more, but this may only serve to occlude the upper airway further, leading to more sleep loss. As such a vicious cycle of sleep loss and increased food intake may be occurring in these patients. OSA may be associated with resistance to the weight reducing effects of leptin [115, 116], which may in turn result in increased appetite and weight gain.

Recent data show that hypocretin is involved in the control of upper airway patency [117]. Hypocretin neurons project to respiratory centers in the brainstem, which express hypocretin receptors, and where injection of hypocretin stimulates breathing [118]. In hypocretin knockout mice, there is a 50% reduction in CO_2-induced increases in breathing and these mice have more spontaneous sleep apneas [119, 120]. In wild-type mice, inhalation of CO_2 increases activity of hypocretin neurons as determined by c-FOS labeling [121]. In vitro studies have found increased activity of identified hypocretin neurons in response to acidity [122].

Hypocretin levels have been measured in OSA but with mixed results. One study reported a positive correlation between an apnea–hypopnea index and hypocretin levels [123], whereas another study found that the levels were low in OSA [124]. Levels of histamine have been measured in OSA and not different from controls indicating that CSF histamine is a biomarker reflecting the degree of hypersomnia of central origin [125].

Conclusion

A distributed network of neurons from the preoptic area to the pons is responsible for generating waking, non-REM sleep, and REM sleep. The discovery of hypocretin, its link with waking and the fact that these neurons are located in the part of the brain that also regulates energy metabolism, provides a way to understand disorders where the major symptoms are feeding disturbance, loss of sexual drive, abnormality in endocrine rhythms, hypersomnia, and short REM sleep latency. As we noted in the review, receptors that regulate appetite are found on neurons that generate sleep and wakefulness. As such, pharmacological agents that curb appetite are likely to also impact sleep and wakefulness.

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