Neurobiology of the Control of Sleep

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Introduction

Two biological processes have been thought to independently regulate the timing and length of sleep: process C and process S. This two-process model of sleep regulation was first proposed in 1982 by a Swiss sleep researcher, Alexander Borbely [1]. Process C, the circadian process, refers to the roughly 24-hour sleep-wake cycle. Research in the 1970s determined that the suprachiasmatic nucleus (SCN) of the hypothalamus was capable of autonomous oscillation and was later found to be the primary controller of this circadian process [2]. Process S, or the homeostatic process, determines that the propensity to sleep is also based on the previous amount of wakefulness and sleep [3]. These two processes have different regulatory mechanisms. The main markers of process C are core body temperature (CBT) and melatonin [4]. The main markers of process S are

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non-rapid eye movement (NREM) sleep and slow wave activity (SWA) [5]. In the classic two-process model theory, when process S approaches the upper threshold of process C, sleep occurs. Conversely, wakefulness occurs when process S approaches the lower threshold of process C. These two processes are illustrated in Fig. 3.1 [1]. In the last two decades, new scientific findings have helped expand our knowledge of sleep regulation, recognizing that sleep homeostasis not only is a global brain process but also presents regional variations. Regional brain differences in the sleep electroencephalography (EEG), for example, can have implications on the markers of process S, as low-frequency power is predominant in the frontal derivations. The discovery of the circadian genes has moved research of sleep to the molecular/genetic level, showing that both processes have more complex interactions than what we initially thought. Sleep stages, on the other hand, are regulated by ultradian cycles. This refers to a particular order in which sleep stages occur and cycle through the night. In this chapter, we will discuss the two-process model, how process C and process S regulate sleep, and a brief introduction to the ultradian rhythm.

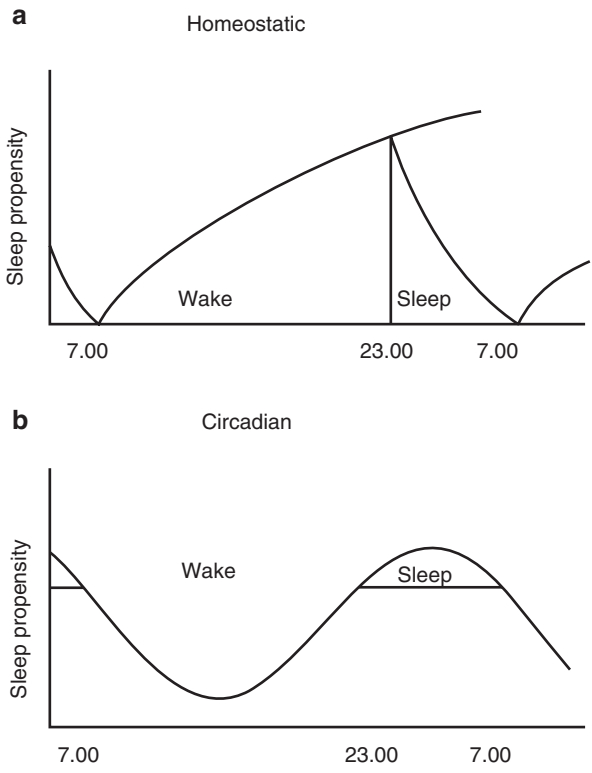

Fig. 3.1 (**a**) Homeostatic control of sleep. (**b**) Circadian control of sleep. (From Borbely [1])

Circadian Rhythm

Circadian Anatomy

The Pacemaker: The Suprachiasmatic Nucleus

The rest/activity cycle in most animals exhibits a 24-hour rhythm that is synchronized mainly to the light-dark cycle. In the absence of light or in the absence of any environmental cues, the circadian rhythms persist in free-running cycles that last a little longer than 24 hours in humans. Early studies have identified the suprachiasmatic nucleus (SCN) is the primary circadian oscillator [6]. The SCN is located in two small areas of the hypothalamus, located just superior to the optic chiasm, on either side of the third ventricle. Destruction of this area causes loss of circadian rhythmicity of the rest/activity cycle. In the majority of cases, the destruction is done experimentally in animals [7, 8]. In humans, accidental destruction of the SCN has been reported in a woman who suffered a gunshot wound that affected both optic nerves and suprachiasmatic nucleus resulting in irregular sleep-wake cycle as seen in Fig. 3.2 [9].

The paired right and left SCN each contains approximately 10,000 neurons that express circadian rhythmicity. They include neurons that synthesize γ-aminobutyric acid (GABA) among other peptides and neurotransmitters [10]. The SCN has been

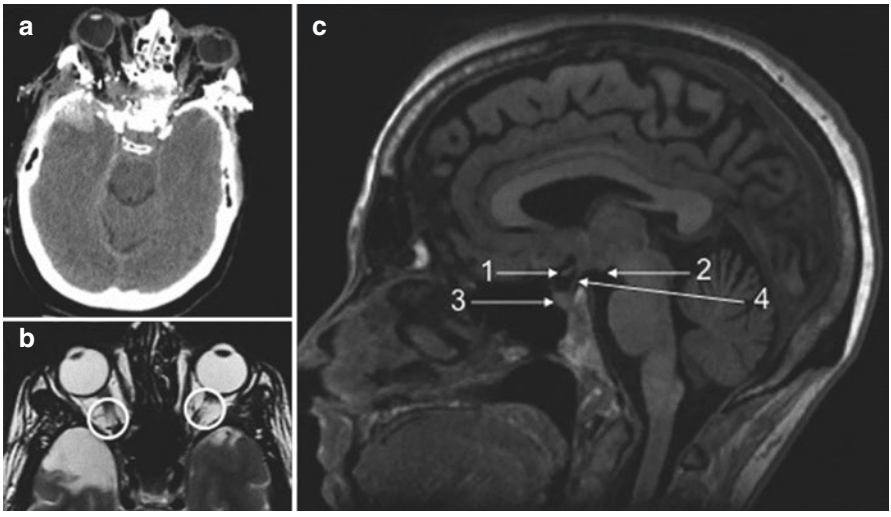

Fig. 3.2 (**a**) Computerized tomography of the head showing damage of the optic nerves bilaterally following a gunshot wound to the right temple. Note bone fragments along the bullet path across the suprachiasmatic area. (**b**) Axial T2-weighed magnetic resonance imaging (MRI) of the head showing bilateral optic nerve hyperintensities consistent with nerve damage (circles). (**c**) Sagittal T1-weighted MRI of the head. The optic chiasm (arrow 1) forms the anterior boundary of the hypothalamus. The infundibulum (arrow 4) to the pituitary gland (arrow 3) and the mammillary bodies (arrow 2) form the inferior boundary of the hypothalamus. The optic chiasm appears thinned along with the adjacent hypothalamus. (From DelRosso et al. [9])

traditionally divided into a ventrolateral area that synthesizes vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) and a dorsomedial area that synthesizes vasopressin (VP), substance P, and somatostatin [11]. Another functional organization of the SCN refers to these areas as a shell (dorsomedial) and a core (ventrolateral) [12]. The core receives most of the light signal input from the retina.

Circadian Afferents

The major input to the SCN is from the retinohypothalamic tract (RHT). Photic information is received by ganglion cell receptors in the retina and transmitted to the SCN. These signals activate GRP and VIP cells in the core of the SCN. Research has shown that VIP release plays a pivotal role in circadian synchronization [13]. In the absence of VIP or the VIP receptor VIPC2R [14], the neurons in the SCN do not synchronize affecting many rest/activity cycles [15].

A secondary pathway by which light information reaches the SCN arises from the intergeniculate leaflet (IGL) and is called the geniculohypothalamic tract (GHT). The GHT neuron terminals release GABA and neuropeptide Y, and it is thought to play a role in transmitting the effect of more subtle photic stimuli and non-photic stimuli such as metabolic inputs to the SCN [16, 17].

Other afferent pathways to the SCN include serotonin-producing neurons projecting from the raphe nucleus, noradrenergic neurons from the locus coeruleus, histaminergic neurons from the posterior hypothalamus, and cholinergic projections from the pontine tegmentum and basal forebrain (BF). Recent evidence suggests that the SCN receives information directly or indirectly from about 80 different areas in the brain (Fig. 3.3) [18].

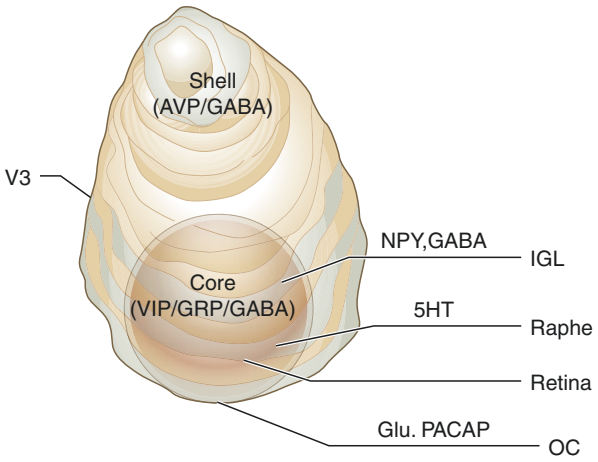

Fig. 3.3 Schematic of SCN with major afferents and associated neurotransmitters. *AVP* arginine vasopressin, *GABA* gamma-aminobutyric acid, *VIP* vasoactive intestinal peptide, *GRP* gastrin-releasing peptide, *NPY* neuropeptide Y, *5HT* serotonin, *Glu* glutamate, *OC* optic chiasm, *PACAP* pituitary adenylate cyclase-activating polypeptide, *IGL* intergeniculate leaflet, *Raphe* raphe nucleus. (Modified from Honma [46])

Circadian Efferents

The SCN has three major output pathways: (1) the rostral pathway to the preoptic area and paraventricular nucleus of the thalamus, (2) caudally to the retrochiasmatic area and ventromedial nucleus, and (3) to the ventral subparaventricular zone (SPZ) and to the hypothalamic paraventricular nucleus (PVN). From the PVN, signals synapse in the preganglionic sympathetic neurons of the spinal cord where melatonin secretion is regulated. The most dense pathway is to the SPZ. Lesions to the ventral part of the SPZ abolish circadian rhythms, and lesions in the dorsal SPZ affect body temperature. The ventral SPZ projects to the dorsomedial hypothalamus (DMH) that in turn connects to other areas involved in sleep and wakefulness. The largest projection is to the ventrolateral preoptic nucleus (VLPO), a group of sleep-active neurons that has inhibitory input to the major ascending arousal systems during sleep; lesions of the VLPO are associated with insomnia.

The function of the circadian clock can be simplistically summarized into three main areas: generation of the circadian rhythms, entrainment of the circadian rhythms, and coupling of the circadian rhythm with the social sleep-wake cycle. We will discuss these functions and how they are accomplished in the following sections.

Circadian Physiology

Generation of Circadian Rhythms

Over the past 20 years, the understanding of the molecular mechanism of circadian rhythmicity has increased. The SCN generates spontaneous oscillations by feedback loops of translation and transcription of circadian genes. This feedback cycle is cell-autonomous and allows for adaptability. Feedback manipulation of circadian genes can lead changes in timing, quality, and quantity of sleep. The firing frequency of the SCN is 6–10 Hz during the day and <1 Hz at night. The first circadian gene identified was called Clock (circadian locomotor output cycles kaput), which codes for a transcription factor CLOCK which plays a role in the persistence and period of circadian rhythms [19]. Other major circadian genes are Per, Cry, and Bmal1. While CLOCK is constitutively expressed with minimal circadian variability in protein levels, PER, CRY, and BMAL1 all have a diurnal pattern of expression [19].

There are multiple levels of feedback loops within this system (Fig. 3.4). The PER and CRY proteins form a complex that indirectly provide inhibition of the activation of the Per and Cry genes. Conversely, the complex formed by the activators BMAL1 and CLOCK enhances expression of Per and Cry. Binding of the PER-CRY complex to the BMAL1-CLOCK complex prevents the expression of Per and Cry. Likewise, Bmal1 expression undergoes feedback inhibition by its product, BMAL1, via the product of the Rev-Erba gene. When the PER-CRY complex binds to BMAL1-CLOCK, it reduces transcription of Rev-Erba, thus indirectly enhances Bmal1 expression. The net effect is that PER and CRY are expressed more in the daytime, and the formation of their complex inhibits activity of CLOCK-BMAL1. Then in the circadian night, PER and CRY are degraded, leading to a repeat of the

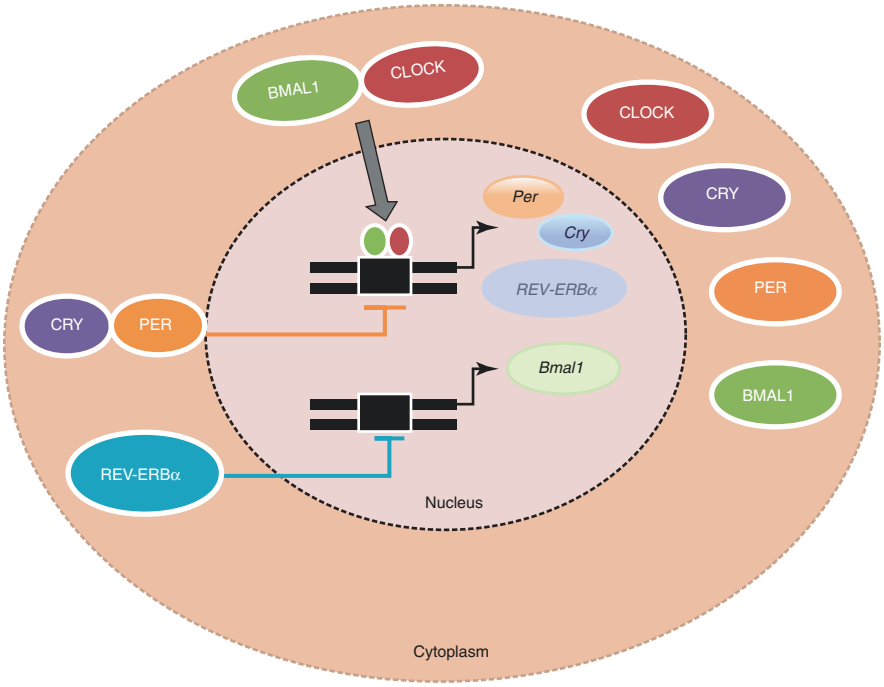

Fig. 3.4 Model of the circadian clock in mammals. CLOCK and BMAL1 act as master transcription factors to regulate (1) the Per and Cry genes in the core feedback loop of the clock, (2) the REV-ERB/ROR feedback loop regulating Bmal1 transcription, and (3) thousands of target genes that are clock outputs. The stability of the PER and CRY proteins is tightly regulated by E3 ubiquitin ligases in both the cytoplasm and nucleus that determine circadian period. (From Krakowiak and Durrington [47])

cycle with next turn of the circadian clock [20]. There are additional molecular cascades downstream that further sculpt and refine circadian output.

Mutations or manipulation of circadian genes can lead changes in timing, quality, and quantity of sleep; for example, mutations of Clock can alter circadian period, and mutations of Bmal1 can abolish circadian rhythmicity.

Circadian rhythms are not isolated to the control of sleep. It is estimated that 20–40% of genes have some circadian periodicity to them, although most oscillate in only one organ. While about 3% of genes in the hypothalamus have a circadian pattern of expression, other organs, including the liver, kidney, and lung, have more than 10% of genes expressed in a circadian pattern [21]. Circadian regulation of gene expression is not limited to the transcriptional processes but includes every regulatory step in gene expression, including splicing, transcriptional termination, polyadenylation, nuclear/cytoplasmic transport, miRNA

regulation, translation, protein phosphorylation, and RNA degradation [22, 23]. A substantial fraction of genes in any cell or tissue undergo circadian oscillations at the mRNA level. In a recent publication on a diurnal transcriptome atlas of a primate across major neural and peripheral tissues, 82% of genes were found rhythmic in at least one tissue. Hence, regulation of circadian gene expression includes both transcriptional and posttranscriptional mechanisms, which in turn can be modulated by various factors (including metabolic ones) interacting with these processes [24]. Misalignment of circadian patterns across organ systems can contribute to human disease and disability. For example, the role of circadian rhythms in metabolism and metabolic disorders has been extensively studied. This is reflected in a known connection between shift work and metabolic diseases. One related finding is that 10 days of circadian asynchrony can lead to insulin resistance and increased fat deposition in humans.

Circadian Entrainment

Circadian rhythms are a part of organisms. In fact they exist naturally in the absence of any external stimuli but can be entrained to adapt to changing photoperiods or changes in social, ecologic, or behavioral conditions. Phase control of the circadian clock is achieved by "zeitgebers." Zeitgebers (literally "time givers" in German) are defined as environmental cues that synchronize or reset the circadian clock. Light is the most powerful zeitgeber. Others include food, sound, temperature, and even stress or social interactions. Entrainment of circadian rhythms starts occurring in the first few months of life as infants. The SCN is cycling at birth, but entrainment to the external environment occurs in the first few weeks of life. By 3 weeks there is a difference between day and nighttime sleep durations and associated diurnal changes in body temperature [25].

The physiologic process of entrainment to light cues begins when melanopsin-containing photosensitive ganglion cells on the retina receive light signals and transmit them via the RHT to the SCN where activation of nerve endings releases glutamate. Glutamate acts on N-methyl-D-aspartic acid (NMDA) and non-NMDA receptors to increase Per gene expression. Experimental exposure of the SCN to glutamate mimics the effect of light. Light activation of the SCN produces an influx of calcium and activation of Per genes.

The RHT also projects to the anterolateral hypothalamus, subparaventricular zone, supraoptic region, and intergeniculate leaflet of the thalamus. RHT also releases substance P and pituitary adenylate cyclase-activating peptide (PACAP), both of which play a role in circadian rhythm shifts. Damage to rods and cones in mice does not affect the circadian cycle, but removal of the melanopsin-containing retinal ganglion cells abolishes circadian entrainment.

Destruction of the SCN abolishes rhythmicity, resulting in an "irregular sleep-wake rhythm disorder." Patients with neurodegenerative disorders like Alzheimer's disease are at increased risk. The author reported a unique case of a

38-year-old woman with a gunshot wound to the head that severed both optic nerves (Fig. 3.2). The woman exhibited an irregular pattern of sleep and wakefulness with an estimated average total sleep time of 8.8 hours per 24-hour period. Polysomnography hypnogram corresponding to day 1 of actigraphy demonstrated fragmented sleep-wakefulness pattern that was not completely identified by actigraphy alone.

Circadian Coupling Disorders

Circadian dysregulation occurs when there is an abnormal phase in the sleep-wake cycle. The *International Classification of Sleep Disorders Third Edition* [26] criteria for circadian rhythm sleep-wake disorder include a disruption in the sleep-wake period either due to a change in the endogenous circadian timing or due to a misalignment between the circadian clock and the socially desired sleep-wake cycle. This misalignment in circadian timing must cause sleep-related symptoms such as insomnia, excessive sleepiness, or both. Circadian rhythm disorders are divided into advanced sleep-wake-phase disorder (ASWPD), delayed sleep-wake-phase disorder (DSWPD), irregular sleep-wake disorder, non-24-hour sleep-wake disorder, shift work disorder, jet lag disorder, and circadian sleep-wake disorder not otherwise specified [26].

ASWPD can be seen when sleep occurs earlier than desired sleep times as seen with familial advanced sleep-phase syndrome (FASPS). This is also seen with advanced age.

In DSWPD sleep periods occur later than desired as seen with the delayed sleep-phase syndrome (DSPS). When the sleep-wake cycle is quasiperiodic, following a nearly 24-hour cycle, but free running around the clock with lack of entrainment to light-dark cycles, this can be seen in non-24-hour sleep-wake syndrome, as seen in those with total blindness, with inability for light signal to reach the SCN (not seen in cortical blindness where the retinal ganglion pathway to the SCN remains intact).

Markers of Process C

Dim Light Melatonin Onset

Melatonin secretion from the pineal gland peaks in the evening, signaling readiness for sleep onset. Melatonin induces vasodilation and is associated with the subjective feeling of drowsiness.

Body Temperature

Body temperature declines, and core body temperature (CBT) reaches its nadir during night sleep. CBT is the temperature of the brain and internal organs and is subject to circadian oscillations [27, 28]. The explanation for the relationship between the thermoregulatory systems and sleep regulatory system is likely that of sleep's purpose of energy conservation. The overall regulation of CBT is affected by both

the circadian and homeostatic processes. A rostral projection from the SCN to the preoptic anterior hypothalamus conveys the circadian signal to the thermoregulatory system as melatonin endogenously downregulates CBT as it rises in the evening [29, 30]. Heat distribution from the core to the periphery is completed during the third sleep cycle resulting in the nadir CBT. Of note, this thermoregulatory system is not active during REM sleep, and body temperature during REM sleep actually rises due to increased metabolic activity.

Body temperature, like melatonin, is also controlled by environmental cues, one of the major cues being body position. In the supine body position, blood is redistributed together with heat, from the core to the periphery resulting in increased skin temperature and decreased CBT, thus increasing sleepiness (e).

Cortisol

Sleep onset is associated with short-term inhibition of cortisol secretion, particularly during slow wave sleep. Cortisol then rises dramatically before the waking period and is regulated by the circadian process. SCN neurons project both directly and indirectly to the dorsomedial hypothalamic nucleus (DMH), which then sends efferent neurons to the PVH. There are corticotropin-releasing hormone-containing neurons in the PVH that project to the median eminence where corticotropin-releasing hormone is released to circulation activating the release of cortisol from the anterior pituitary. The adrenocorticotropic hormone in the blood then results in rhythmic induction of corticosteroid secretion from the adrenal gland [31].

Homeostatic Control of Sleep

Process S refers to sleep homeostasis, wherein accumulated time spent awake leads to increasing sleep pressure. The pressure of this sleep debt then decreases during sleep. Under typical diurnal human conditions, this sleep pressure rises and falls entrained to day and night. When S approaches a lower boundary, it triggers wake. As it approaches an upper boundary, sleep is triggered.

Anatomy

Adenosine is the major neuromodulator felt to be involved in the homeostatic process of sleep. Adenosine inhibits the central nervous system. In cats, the basal forebrain and, to a lesser extent, the neocortex, adenosine increases during sustained waking [32]. Brain adenosine rises when ATP production is reduced. One theory is that increased adenosine is a signal of reduced brain energy reserves that develop during waking and that sleep is induced as an energy-restorative state [33]. Another supporting discovery implicating adenosine's role in sleep homeostasis is that caffeine, a potent alerting agent, is an adenosine antagonist.

Physiology

In 2008, Landolt postulated the role of adenosine in the homeostatic control of sleep. Adenosine has been shown to promote slow wave sleep and rapid eye movement (REM) sleep in animal models. Adenosine accumulates in the extracellular space during wakefulness and acts to inhibit wake-promoting neurons primarily in the basal forebrain via A1 receptors. During sleep, extracellular adenosine levels decline.

Accumulation of adenosine in the basal forebrain has correlated with both increased SWA and sleep duration. Its accumulation therefore corresponds to the degree of sleep pressure [34].

Interestingly, caffeine blocks adenosine receptors, which is proposed as a primary mechanism of its alerting action.

Markers

Markers which correspond to this sleep pressure include non-rapid eye movement (NREM) sleep electroencephalography (EEG) slow wave activity (SWA), which increases under conditions of increasing sleep pressure. Theta activity in waking is a marker of the rising limb of S as one moves toward wakefulness [35].

Process S is impacted by lack of sleep regardless of time of day. For example, NREM sleep SWA during daytime naps increase with duration of prior wakefulness. Following naps, the SWA in that night's sleep period decreases predictably. Suppression of SWA without disturbing sleep has been shown to result in a rebound increase in SWA in the next sleep period. Studies have also shown that increased mental or physical work results in increase of SWA and shorter sleep onset latency, which is also considered a marker of sleep pressure.

Ultradian Rhythm

As we have seen in previous chapters, sleep is not a homogeneous state, but it is divided into different stages with various electroencephalographic and physiologic characteristics. In general terms sleep is divided into non-rapid eye movement (NREM) sleep stage and rapid eye movement (REM) sleep. NREM is further divided into three stages: N1,N2, and N3. As humans fall asleep, they usually enter sleep into N1 and spend few minutes in this stage, as N2 ensures forming a more consolidated sleep, after which N3 appears. After approximately an hour of NREM sleep, the brain usually enters REM sleep. This cycle repeats itself four to five times in a night. REM sleep deprivation studies have also demonstrated that REM sleep is regulated by homeostatic control; however, the mechanism of NREM-REM cycling during sleep remains unknown [36].

Circadian Draining of Waste During Sleep

Clearance of metabolic waste from the brain is essential for CNS homeostasis. The circadian control of this process is indicated by the occurrence of a daily rhythm in the permeability of the blood-cerebrospinal fluid (CSF) barrier, as shown by measuring relative metabolite levels between CSF and blood. Indeed, the choroid plexus, an important component of the blood-CSF barrier, displays circadian clock activity [37], regulating timed fluid exchange between the blood and CSF. In the fruit fly, a circadian clock in glial cells of the hemolymph-brain barrier regulating xenobiotic efflux was demonstrated [38] giving rise to the hypothesis that glial cells including astrocytes regulate blood-brain barrier function and modulate metabolic waste clearance in mammals.

The conventional view of solute movements in the extracellular space (ECS) of the CNS has been based on diffusion, and the mechanisms modulating the variations in the abundance of products to be eliminated have been sought in the coupling of blood flow and metabolism, processes which are influenced by regulators such as biogenic amines, adenosine, NO, H+, and K+. In the last years, a new interpretation has been put forward, i.e., the glymphatic hypothesis [39–41]. The term has been coined to describe the active, lymphatic-like movements in the ECS which occur in the brain. It has been suggested that this process, which is normally dependent on the activity of lymphatic vessels, can nevertheless take place in the brain, which is devoid of such vessels, because of water exchange. More specifically, it has been hypothesized that solute movement is driven by perivascular astrocytes, which are strongly enriched in aquaporin-4 (AQP4), and by changes in the vascular lumen. AQP4 is predominantly expressed in the end feet of these astrocytes. Water release via AQP4 may be responsible for an actively driven fluid exchange between para-arterial and paravenous spaces, connected by a convective flow through the other parts of the ECS, especially concerning the interstitial fluid. Additionally, it has been assumed that arteriolar pulsations as well as respiration-dependent venular collapse and reinflation may further enhance the flow through occurring in the ECS [42].

Sleep-related variations in cerebral waste products were described [38–40]. The elimination of amyloid β peptide (Aβ) has been reported to be considerably enhanced during sleep [43]. The concept of glymphatic Aβ clearance has received support from the observation that elimination of injected radiolabeled Aβ peptide was strongly reduced in AQP4−/− mice [39].

The exchange of solutes between the CSF and the interstitial fluid occurs mostly during NREM sleep when the cortical interstitial space increases by more than 60% and provides a low resistance path for the movement of CSF and interstitial fluid in the brain parenchyma. The contribution of the glymphatic system to the repair function of sleep has been discussed in relation to age-associated deviations from the normal sleep profile, including decreased and delayed CSF penetration of fluid along perivascular pathways and pial surface [44]. Various neurological disease

states such as stroke, traumatic brain injury, and AD have been interpreted in terms of the contribution by glymphatic dysfunction [42]. Altogether, the data indicate that the circadian clock regulates a variety of crucial processes in the brain, including sleep, brain metabolism, and maintenance of flow balance of compounds into and out of the brain. Disruption of the circadian clock, and/or any of the signaling pathways regulated by it, can lead to inefficient anabolic and catabolic biochemical processes [45].

Conclusion

In this chapter we have discussed the processes that control and regulate sleep. Far from a quiet state, sleep is orchestrated by circadian, ultradian, and homeostatic regulation. We discussed the role of the suprachiasmatic nucleus as the pacemaker of the circadian rhythm and the entrainment with light and melatonin. Circadian sleep disorders occur when there is a misalignment between the internal pacemaker and the socially established sleep time, causing significant nighttime or daytime dysfunction. Prolonged awakening increases sleep pressure during homeostatic control. REM and NREM occur during cycles in sleep, and finally, clearance of metabolic waste from the brain is essential to keep a healthy homeostatic process.

References

1. Borbely AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1(3):195–204.
2. Ibuka N, Kawamura H. Loss of circadian rhythm in sleep-wakefulness cycle in the rat by suprachiasmatic nucleus lesions. Brain Res. 1975;96(1):76–81.
3. Knowles JB, Coulter M, Wahnon S, Reitz W, MacLean AW. Variation in process S: effects on sleep continuity and architecture. Sleep. 1990;13(2):97–107.
4. Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int. 1989;6(1):93–102.
5. Finelli LA, Baumann H, Borbely AA, Achermann P. Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. Neuroscience. 2000;101(3):523–9.
6. Moore RY, Eichler VB. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. Brain Res. 1972;42(1):201–6.
7. Ibuka N, Nihonmatsu I, Sekiguchi S. Sleep-wakefulness rhythms in mice after suprachiasmatic nucleus lesions. Waking Sleeping. 1980;4(2):167–73.
8. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci U S A. 1972;69(6):1583–6.
9. DelRosso LM, Hoque R, James S, Gonzalez-Toledo E, Chesson AL Jr. Sleep-wake pattern following gunshot suprachiasmatic damage. J Clin Sleep Med. 2014;10(4):443–5.
10. Antle MC, Silver R. Orchestrating time: arrangements of the brain circadian clock. Trends Neurosci. 2005;28(3):145–51.
11. Morin LP, Allen CN. The circadian visual system, 2005. Brain Res Rev. 2006;51(1):1–60.

12. Moore RY. The suprachiasmatic nucleus and the circadian timing system. Prog Mol Biol Transl Sci. 2013;119:1–28.
13. An S, Harang R, Meeker K, Granados-Fuentes D, Tsai CA, Mazuski C, et al. A neuropeptide speeds circadian entrainment by reducing intercellular synchrony. Proc Natl Acad Sci U S A. 2013;110(46):E4355–61.
14. Harmar AJ, Marston HM, Shen S, Spratt C, West KM, Sheward WJ, et al. The VPAC (2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei. Cell. 2002;109(4):497–508.
15. Colwell CS, Michel S, Itri J, Rodriguez W, Tam J, Lelievre V, et al. Disrupted circadian rhythms in VIP- and PHI-deficient mice. Am J Physiol Regul Integr Comp Physiol. 2003;285(5):R939–49.
16. Rosenwasser AM, Turek FW. Neurobiology of circadian rhythm regulation. Sleep Med Clin. 2015;10(4):403–12.
17. Saderi N, Cazarez-Marquez F, Buijs FN, Salgado-Delgado RC, Guzman-Ruiz MA, del Carmen BM, et al. The NPY intergeniculate leaflet projections to the suprachiasmatic nucleus transmit metabolic conditions. Neuroscience. 2013;246:291–300.
18. Morin LP. Neuroanatomy of the extended circadian rhythm system. Exp Neurol. 2013;243:4–20.
19. Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, et al. Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. Science. 1994;264(5159):719–25.
20. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci. 2018;19(8):453–69.
21. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci U S A. 2014;111(45):16219–24.
22. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet. 2017;18(3):164–79.
23. Mure LS, Le HD, Benegiamo G, Chang MW, Rios L, Jillani N, et al. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. Science. 2018;359(6381) https://doi.org/10.1126/science.aao0318.
24. Mermet J, Yeung J, Naef F. Systems chronobiology: global analysis of gene regulation in a 24-hour periodic world. Cold Spring Harb Perspect Biol. 2017;9(3):a028720.
25. Hellbruegge T, Lange JE, Stehr K, Rutenfranz J. Circadian periodicity of physiological functions in different stages of infancy and childhood. Ann N Y Acad Sci. 1964;117:361–73.
26. American Academy of Sleep Medicine. International classification of sleep disorders 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
27. Krauchi K. The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. Sleep Med Rev. 2007;11(6):439–51.
28. Tayefeh F, Plattner O, Sessler DI, Ikeda T, Marder D. Circadian changes in the sweating-to-vasoconstriction interthreshold range. Pflugers Arch. 1998;435(3):402–6.
29. Moore RY, Danchenko RL. Paraventricular-subparaventricular hypothalamic lesions selectively affect circadian function. Chronobiol Int. 2002;19(2):345–60.
30. Krauchi K, Cajochen C, Pache M, Flammer J, Wirz-Justice A. Thermoregulatory effects of melatonin in relation to sleepiness. Chronobiol Int. 2006;23(1–2):475–84.
31. Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. J Neurosci. 2003;23(33):10691–702.
32. Thakkar MM, Winston S, McCarley RW. A1 receptor and adenosinergic homeostatic regulation of sleep-wakefulness: effects of antisense to the A1 receptor in the cholinergic basal forebrain. J Neurosci. 2003;23(10):4278–87.
33. Benington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol. 1995;45(4):347–60.
34. Mabuchi H, Nakahashi H. A major inhibitor of phenytoin binding to serum protein in uremia. Nephron. 1988;48(4):310–4.

35. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. J Sleep Res. 2016;25(2):131–43.
36. Weber F. Modeling the mammalian sleep cycle. Curr Opin Neurobiol. 2017;46:68–75.
37. Myung J, Schmal C, Hong S, Tsukizawa Y, Rose P, Zhang Y, et al. The choroid plexus is an important circadian clock component. Nat Commun. 2018;9(1):1062.
38. Zhang SL, Yue Z, Arnold DM, Artiushin G, Sehgal A. A circadian clock in the blood-brain barrier regulates xenobiotic efflux. Cell. 2018;173(1):130–9. e10
39. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012;4(147):147ra11.
40. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. J Clin Invest. 2013;123(3):1299–309.
41. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic system: a Beginner's guide. Neurochem Res. 2015;40(12):2583–99.
42. Nedergaard M. Neuroscience. Garbage truck of the brain. Science. 2013;340(6140):1529–30.
43. Boespflug EL, Iliff JJ. The emerging relationship between interstitial fluid-cerebrospinal fluid exchange, amyloid-beta, and sleep. Biol Psychiatry. 2018;83(4):328–36.
44. Zeppenfeld DM, Simon M, Haswell JD, D'Abreo D, Murchison C, Quinn JF, et al. Association of Perivascular Localization of Aquaporin-4 with cognition and Alzheimer disease in aging brains. JAMA Neurol. 2017;74(1):91–9.
45. Albrecht U, Ripperger JA. Circadian clocks and sleep: impact of rhythmic metabolism and waste clearance on the brain. Trends Neurosci. 2018;41(10):677–88.
46. Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J Physiol Sci. 2018;68(3):212.
47. Krakowiak K, Durrington H. The role of the body clock in asthma and COPD: implication for treatment. Palm Ther. 2018;4:29–43. Received May 1, 2018. Published online June 21, 2018. https://doi.org/10.1007/s41030-018-0058-6.