SLEEP

Dag Stenberg
Institute of Biomedicine/Physiology, University of Helsinki, Finland

Keywords: Adenosine, insomnia, learning and memory, sleep center, sleep stages, REM sleep, transmitters, wakefulness

Contents

Summary

All species sleep or have a recurring resting phase which resembles sleep. Mammalian sleep is divided into non-REM and REM sleep, which may serve different functions. Sleep structure and brain mechanisms are remarkably similar between vertebrate species. Many features are also common to invertebrates. Sleep may occur during dark or during light, and it is regulated partly by a circadian rhythm, partly according to need. In humans, the most common sleep disorders are insomnia and obstructive sleep apnea, but other common problems include narcolepsy and sleep disturbances called parasomnias. Brain research has revealed multiple waking regulatory centers, but only a few sleep-active areas in the brain.

The neurotransmitters noradrenaline, histamine, acetylcholine and serotonin, as well as the neuropeptide hypocretin/orexin, have important roles in waking, while gamma-aminobutyric acid is involved in sleep promotion. The neuromodulator adenosine is a prominent homeostatic regulator of sleep, and may signal incipient energy depletion in a critical brain area, possibly involving nitric oxide. Other sleep-promoting substances in the brain comprise interleukin-1 and growth hormone-releasing hormone.

The ubiquity and homeostatic regulation of sleep indicate a vital significance, which may be related to brain energy balance and/or the maintenance of synaptic connections not normally used during waking. In addition, several additional brain and body functions may have been coupled to sleep and are normally favoured by or even dependent on sleep. Such functions include learning and memory, development and plasticity, and hormonal balance.

1. Introduction

All living organisms show oscillation between rest and activity. In animals ranging from fruit flies to humans, phases of behavioral rest are characterized by heightened threshold to stimuli, indicating decreased or changed brain activity ("sleep"). The longer the preceding activity period has been, the longer and more intense is the following period of rest or sleep. If an animal is deprived of sleep for an extended period, there follows sickness and possibly death. This indicates a fundamental need for sleep in an individual. "Sleep" has been defined in birds and mammals by electrographic criteria, but these are not applicable to other species. Figure 1 depicts the main components of the human brain.

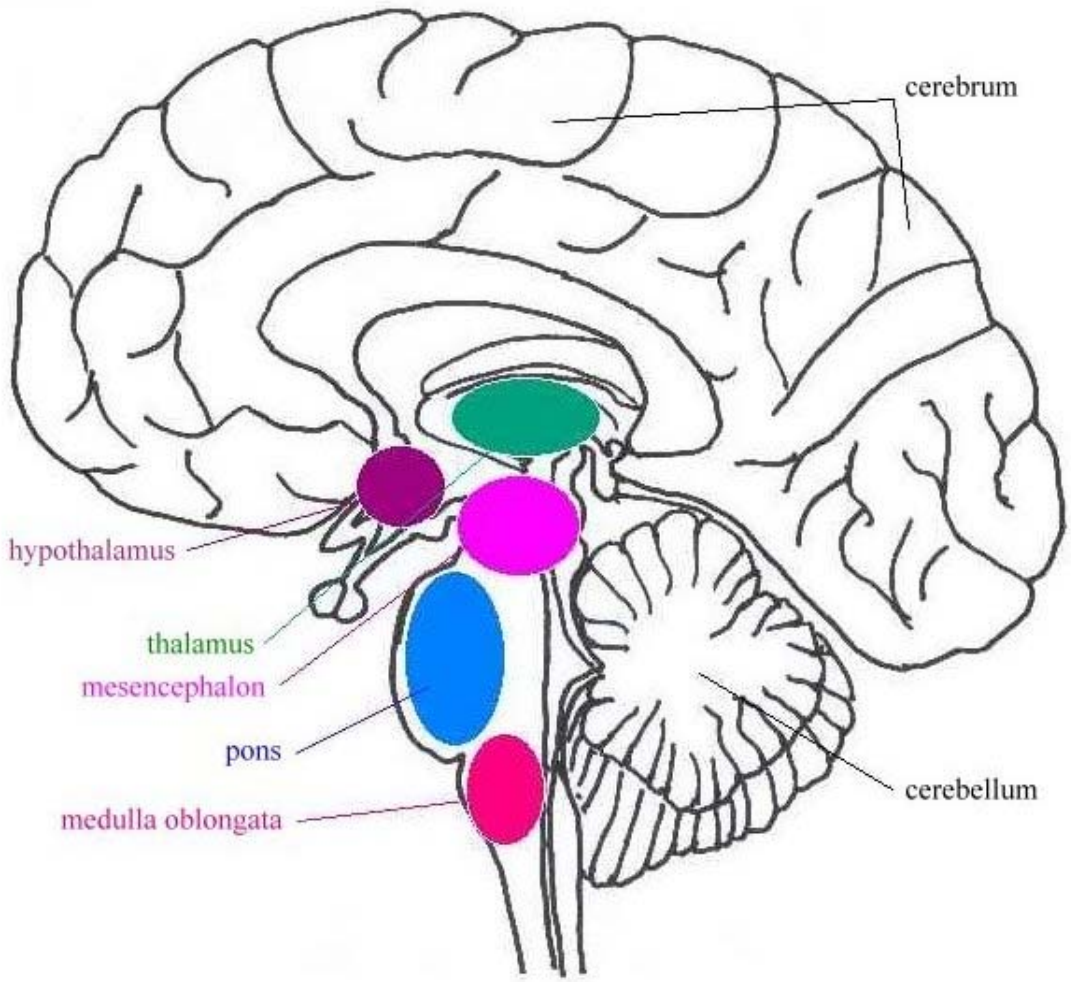

Figure 1. The human brain and its sizeable cerebrum and cerebellum as well as deeper structures thalamus, hypothalamus, mesencephalon, pons and medulla oblongata which continues as spinal cord. They all contribute to the regulation of all our activities.

Bird and mammalian sleep is divided into rapid-eye-movements (REM) sleep and non-REM sleep. This distinction is difficult in other species. Many neurochemical correlates of "sleep" are similar in different species, and this fundamental similarity between "sleep" in all studied species indicates a vital role for sleep.

2. Definition of Sleep

Sleep is defined as a physiological (normal) state, in which 1) there is little spontaneous movement, 2) the transmission of sensory stimuli to the brain is diminished and the threshold for awakening increased, 3) the immediate awareness of the surroundings disappears and after awakening one usually does not know how long one has slept, 4) strong stimuli always wake up the individual, as opposed to narcosis or coma.

3. Amount and Timing of Sleep

Adult humans sleep an average of 8 hours per night, but there is considerable individual

variation, and average amounts between 4 and 11 hours are considered normal. Short sleepers have a greater proportion of deep sleep.

Newborn babies sleep up to 16 h a day, half of the sleep being REM sleep. The amount of sleep decreases during childhood. In mid-puberty the sleep need transiently increases, and the preferred time for sleep is delayed. Around 20 years of age, sleep amounts reach the stable adult level, and the preferred time usually advances. In adults, REM sleep occupies about 20 to 25% of sleep time. Aged people often sleep less during the night and take more naps, but the total sleep per 24 hours decreases little.

In the Western culture, adult humans have monophasic sleep (sleep once per 24 h), and sleep is during the dark period. Newborns have polyphasic sleep like most animals. During the first year the sleep phases merge and are shifted to night-time. Afternoon naps persist till school-age. In hot climates, afternoon naps are common in adults. In exceptional circumstances (like single-handed circumnavigation) adults adapt quite easily to a polyphasic sleep schedule.

The propensity for sleep varies with the time of day. When subjects were allowed 7 minutes of bed rest every 20 minutes, during which time they either attempted sleep or were told to resist sleep, their propensity to sleep increased abruptly some time before midnight (the "sleep gate"). Early in the evening their sleep propensity was actually decreased compared to the afternoon ("the forbidden zone for sleep"). This pattern was not influenced by whether they resisted or attempted sleep. It is apparent that the time of day has a strong influence on the timing of sleep.

4. Sleep Stages and the Structure of Nocturnal Sleep

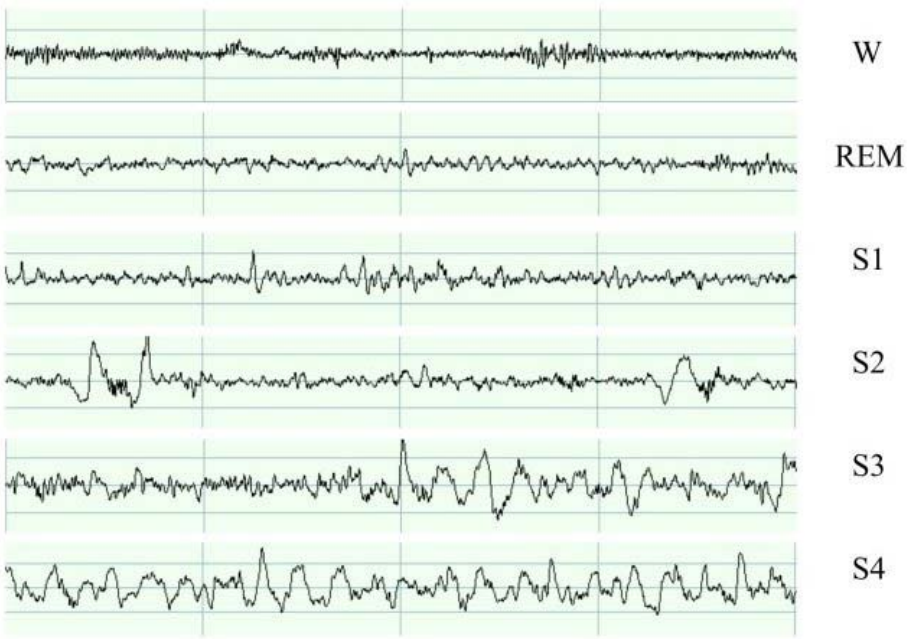

Figure 2. The human EEG in different vigilance stages (wakefulness, REM sleep, nonREM sleep stages S1-S4). Courtesy of A.S. Urrila 2004.

Sleep can be divided into two different states, which alternate 3 to 5 times during the night: REM sleep and non-REM sleep. REM sleep is characterized by rapid eye movements, muscle twitches overriding otherwise quite relaxed muscles, and an electroencephalographic (EEG) (see Figure 2) record resembling wakefulness or drowsiness. About 85% of subjects awoken during REM sleep say they were dreaming, but only about half of our dreams occur during REM sleep. However, dreams seem to occupy less of the time spent in non-REM sleep.

During REM sleep, heart rate and blood pressure are very variable. The respiration is also irregular. In REM sleep, body temperature cannot be well regulated, and REM sleep is indeed impossible in a too warm or too cold surrounding. The brain temperature increases, and energy metabolism is intense in some brain areas.

Non-REM sleep is more restful: the parasympathetic nervous system dominates over the sympathetic, body metabolism slows down, body and brain temperatures decrease, respiration is usually regular, and the reactivity of the organism to stimuli is diminished. Energy metabolism diminishes in several brain areas, including the frontal lobe. Based on brain electrical activity and arousability, the non-REM sleep state is subdivided into stages 1 to 4. Stages 3 and 4 are called slow-wave sleep (SWS) because of the large, slow delta waves in the electroencephalogram.

During a normal night's sleep of 8 hours, about two hours are REM sleep and two hours SWS, while the rest is mainly non-REM stage 2. The method with which the sleep stages can be measured is called polysomnography. Non-REM sleep and REM sleep alternate with a 1.5 hour cycle. During the first half of the night, non-REM episodes are longer and most if it is SWS, but towards morning, REM sleep episodes get longer and longer, while non-REM sleep episodes consist mostly of stage 2 sleep. Short sleepers have a smaller proportion of stage 2 sleep.

5. Regulation of Sleep

5.1. Sleep Need and Homeostasis

Sleeping less than one's individual preference leads to sleep debt, and when one is again allowed the opportunity to sleep, there is a sleep rebound, where part of the lost sleep is regained. These facts indicate a fundamental role for sleep. Indeed, sleep debt is accumulated if we habitually sleep less than we should, for example during a working week, and we have to regain some of the debt during the weekend. Sleep debt is not only accumulated day by day, it is also stored in the brain, probably as a chemical signal, and sleep debt can be paid off only by sleeping. Current knowledge about the mechanisms of sleep debt is reviewed later in this chapter.

Sleep debt leads to tiredness, to decreased attention, and increased tendency to fall asleep. It also affects reaction times, impairs short-term or working memory and concentration ability. In addition to working memory problems, sleep loss also impairs problem-solving ability and creative thinking. The formation of memory traces is benefited by sleep after a learning task, and study results are impaired if sleep does not follow the task. Logical reasoning and performance in routine tasks are less affected,

but it is increasingly difficult to stay alert. The effect of one night's total sleep loss on the brain has been found to be similar to the effect of a blood alcohol level of 0.1% (one per thousand). Reducing sleep by 3 hours for a week (chronic partial sleep loss) produces the same effect, and takes several days of normal sleep to get rid of. Deprivation of REM sleep only has much less effects.

It was thought that the body did not suffer from sleep debt as much as the brain, but recent research provides opposite evidence. Sleep loss increases the secretion of cortisol, epinephrine and other stress hormones, and cortisol further impairs long-term memory. Sleep loss decreases glucose transport to tissues by decreasing the effects of insulin, and creates a metabolic syndrome resembling type 2 diabetes. Evidence from research on humans indicates that chronic sleep loss is a major risk factor for the development of type 2 diabetes and obesity. In experimental animals that have been deprived of sleep for several weeks, stress-produced symptoms like ulcers and skin lesions occur, and they eventually die. There is no evidence that humans can die of sleep loss, nor is it yet sure that it can cause permanent structural damage to the brain.

Rebound sleep after sleep deprivation contains more SWS than sleep normally, and after total sleep deprivation, SWS is preferred to REM sleep. Also during a normal night's sleep, non-REM sleep dominates during the first half of the night. This is part of the evidence that SWS is more important for normal function than REM sleep or stage 2 sleep. However, REM sleep apparently has an important role in the formation of long-term memory traces, and stage 2 sleep is important for learning a task involving motor coordination.

During the 1990s, sleep habits changed radically in the Western world. Surveys in many countries show that habitual nocturnal sleep has been reduced by 0.5 to 1 hour during the week in both the working population and school-children. Bed times have become several hours later, and consequently the percentage of adults and children complaining of morning tiredness has increased dramatically. As sleep debt leads to decreased performance at work and in school, and as the impaired attention and tendency to fall asleep are recognized hazards in traffic and industry, this reduction in habitual sleep time is a major problem for modern society, of a kind unparalleled in the history of man. When the metabolic syndrome and related diseases are also considered, it is apparent that sleep loss and delayed sleep habits constitute a dangerous epidemic of our time. Because this development is comparatively recent, its full impact has not yet been realized.

5.2. Circadian Regulation of Sleep

While the needs of the brain and body specify the amount of sleep we need, the cycle of daylight and darkness determines the optimal time for sleep. Man is diurnal, and tends to sleep during the dark phase. Mammals have an internal clock mechanism in the brain, situated in the "suprachiasmatic nuclei", SCN. Here an internal rhythm close to 24 hours ("circadian") is maintained through the interplay of several genes and their protein products. The SCN then signals to other parts of the brain and to the body, synchronizing their function to the internal rhythm. We function best when our various body functions are properly synchronized.

The internal circadian rhythm is not accurately 24 hours, but it has to be synchronized from the environment. Otherwise the clock will "free-run", i.e. be out of synchrony with the diurnal alternation between light and dark. This is accomplished by light, acting in the eye on retinal cells containing "melanopsin". These cells send synchronizing signals to the SCN, but the SCN is responsive only during certain times of the day. In the early evening, light delays the internal clock, and in the early morning it advances it. During most of the day, however, the SCN is not responsive to signals from the eye. Thus a person who has come into late habits can only be brought back to normal by light in the late night or morning, whereas staying up late in the evening delays him still further.

The internal rhythm can usually only be shifted by 1 to 2 hours on any one day. If one changes surroundings and needs to adjust more than that, as when flying through several time zones, it takes several days to adjust. It is also normally easier to delay than to advance the internal clock.

Melatonin is a hormone secreted into the blood by the pineal gland in the brain during the dark phase, usually between going to sleep and some hours later. The timing of melatonin secretion is influenced by the timing of dawn and dusk. The SCN send signals to the pineal gland, synchronizing melatonin secretion to the dark. Nocturnal exposure to light promptly inhibits the melatonin secretion, but it returns when the light is turned off. Melatonin can also influence the internal clock in the SCN, being more efficient in advancing the clock than light is. A melatonin pill about six hours before the internal secretion will advance the internal clock by half an hour. Melatonin pills can also synchronize the internal clock of blind people.

5.3. Overall Regulation of Sleep

Sleep amounts and sleep timing result from the interplay of these two regulating factors: the sleep debt accumulating during wakefulness, and the time of day, signalled by the arrival of light in the morning. A third factor is called "sleep inertia", and it means that after a bout of sleep, our performance may be impaired for a while. Thus after a nap we may be especially sleepy and perform badly, but the nap still may lead to improved performance half an hour later, because some sleep debt has been paid off. The mechanism for sleep inertia is unknown.

6. Disorders of Sleep

6.1. Insufficient Sleep—Insomnia

Insomnia is common—more than half of the Western population suffer from it at some time during their life, and 10 to 15% regularly. Most often the reason is not organic. Excitement late in the evening, stress, having care of small children, environmental noise, heat or cold, or an uncomfortable bed are common reasons for temporary insomnia. Anxiety about having to wake up abruptly also contributes. Pain and some diseases also lead to insomnia. Ringing of the ears (tinnitus) can effectively disturb falling to sleep. Chronic insomnia can be a reinforced habit—any reason causing temporary sleep loss can increase the anxiety of sleep loss and thus prevent going to sleep. People suffering from major depression more often wake up early and cannot

sleep again, but this type of insomnia also occurs in psychic stress.

Whereas drugs can sometimes be the solution in temporary insomnia, they tend to lose their effect and are no remedy for chronic insomnia. In the latter case, analyzing the basic problem and directing therapy towards dissolving the reinforcing mechanism is indicated. Everybody profits from sound bed-time habits. These include not going to bed too late, avoiding excitement or work late in the evening, trying to relax during the last hour of wakefulness, a quiet, dark, and temperated bed-room, and a comfortable bed.

6.2. Excessive Sleep - Hypersomnia - Excessive Daytime Sleepiness

True hypersomnia—excessive sleep—is rare. Excessive sleep is usually due to some other disease. Excessive daytime sleepiness (EDS) is becoming more and more common. It can be the result of insufficient sleep, due to, for example, sleep apnea, fragmented sleep, organic disease, treatment with drugs or the abuse of drugs or alcohol. The reason for EDS should be investigated since it is not only a subjective nuisance, but also a hazard in many occupations.

6.3. Narcolepsy

About one in 2000 of the population suffers from narcolepsy. This syndrome is composed of fragmented and shallow night-time sleep, daytime sleepiness with sudden sleep attacks, REM sleep bouts soon after going to sleep, day-time attacks of muscle paralysis, called cataplectic attacks, and occasionally dream-like hallucinations. Not all of the symptoms have to occur. Narcolepsy usually starts before middle age, but all symptoms need not be present from the beginning. The tendency is genetically linked. In narcoleptic animals and humans, a major deficiency has been found in the hypocretin/orexin system (see later in this chapter). Various drug treatments have been proposed to alleviate the symptoms, whereas the basic deficiency still defies therapy.

-
-
-

Bibliography

Berridge C.W. and Waterhouse B.D. (2003). The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews* 42(1), 33-84. [A review of the state of art of knowledge about the noradrenergic activating system]

Cirelli C., Gutierrez C.M. and Tononi G. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron* 41(1), 35-43. [The most recent review of gene function in relation to sleep]

Kilduff T.S. and Peyron C. (2000).The hypocretin/orexin ligand_receptor system: implications for sleep and sleep disorders. *Trends in Neurosciences* 23(8), 359-365. [What hypocretin/orexin has to do with

sleep]

Krueger J.M. and Obál F. (1993). A neuronal group theory of sleep function. *Journal of Sleep Research* 2(2), 63-69. [The synaptic maintenance theory]

Krueger J.M. and Majde J.A. (2003). Humoral links between sleep and the immune system: research issues. *Annals of the New York Academy of Sciences* 992, 9-20. [A review of cytokines and sleep]

Kryger M.H., Roth T. and Dement W.C. (Eds.) (2000). *Principles and Practice of Sleep Medicine*. WB Saunders, 3rd Ed. [An extensive handbook on clinical sleep medicine]

Porkka-Heiskanen T., Kalinchuk A., Alanko L., Urrila A. and Stenberg D. (2003). Adenosine, energy metabolism, and sleep. *Scientific World Journal* 3, 790-798. [A review of what was known about cellular mechanisms of sleep debt in 2003]

Roth T. (1999). New trends in insomnia management. *Journal of Psychopharmacology* 13 (4 Suppl 1), S37-40. [How to treat the most common sleep disorder]

Smith C. (2001). Sleep states and memory processes in humans: procedural versus declarative memory systems. *Sleep Medicine Reviews* 5(6), 491-506. [How different sleep stages influence learning and memory]

Strecker R.E., Morairty S., Thakkar M.M., Porkka-Heiskanen T., Basheer R., Dauphin L.J., Rainnie D.G., Portas C.M., Greene R.W. and McCarley R.W. (2000). Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. *Behavioural Brain Research* 115, 183-204. http://www.elsevier [Review of the experimental evidence for adenosine as a sleep factor]

Biographical Sketch

Dag Stenberg was born in Helsinki in April 1941. M.D. from the University of Helsinki in 1965, Ph.D. from the same University in 1973. Docent in Physiology in 1983.

Research and Teaching Assistant at the Department of Physiology, University of Helsinki between 1962 and 1967, Acting Lecturer 1967-1974. Research Fellow in Physiology at the Karolinska Institutet, Stockholm in 1970. Research topic during this time was developmental neurophysiology. Lecturer in Physiology from 1974 to 1985, turning to research on the physiology and neuropharmacology of sleep from 1977. Appointments as Acting Associate Professor and Professor of Physiology at the University of Helsinki in 1976, 1984, 1988, 1990 and continuously from 1994 to 2004, when retired from the University.

Member of the Board of the Finnish Physiological Society 1979-1984, Vice President of the Finnish Sleep Research Society 1988-1990, 1993-1999, Member of the Board 1999-2000, President 2000-2003. Secretary and Officer of the Board of the European Sleep Research Society 1988-1992, Member of the Scientific Committee of the European Sleep Research Society 1992-1998. Delegate for the ESRS to the World Federation of Sleep Research Societies 1998-2000, Secretary-General of the World Federation of Sleep Research Societies 2001-2003. Member of the organizing committee of several international congresses.

Publications mainly in sleep research. Home page: http://www.helsinki.fi/~stenberg/