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Review Article

Enigma of Slumber

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Abstract

Sleep, a complex array of physiological and behavioural processes, is defined as a reversible behavioural condition of perceptual disentanglement from our surroundings. Sleep psychiatry is a flourishing field of cognitive neuroscience that focuses on myriads of interrelations between sleep remedy and psychiatry. Sleep deprivation studies have established the versatile homeostatic functions of sleep including overt cognitive functioning, learning and memory consolidation. Sleep related problems range from insomnia to Kleine-Levin syndrome. At present, there are many sleep laboratories that are spread over the world and are engrossed in exploring the mysteries of sleep.

Keywords: Sleep; Brain; Sleep disorders

Abbreviations

REM: Rapid Eye Movement; GABA: Gamma Amino Butyric Acid; PRNP: Prion Protein Fatal Familial Insomnia; HCRT: Hypocretin; DQB1: DQ Beta 1; PER2: Period Circadian Protein Homolog; TCRA: TCR Alpha Gene; BDNF: Brain Derived Neurotrophic Factor; CREB: cAMP Response Element Binding Protein

Introduction

Sleep has been rightly portrayed as 'nature's soft nurse' by William Shakespeare. We spend almost about eight hours per day and about one-third of our lives in slumber. Sleep is a state of unconsciousness during which there is altered electrical activity in the cerebral cortex and from which a person can be aroused by external stimuli. Sleep is known to facilitate neurogenesis, neuronal plasticity, learning and memory, especially declarative memory consolidation [1-3]. Sleep improves the functioning of antioxidant systems decreasing oxidative stress and neuronal damage created by wakefulness. Sleep thus preserves the brain in optimal conditions to support the damage occurred in different situations throughout the day and even endorses motor recovery following cerebral stroke. There are three characteristics of sleepiness: introspective sleepiness dealing with self-assessment of our internal state, physiological sleepiness involving our body's biological need to sleep and manifest sleepiness denoting the behavioural component as seen in performance related errors due to lack of sleep [4].

Stages of sleep

Sleep laboratories came into vogue since 1953 when Eugene Aserinsky and Nathaniel Kleitman first reported that sleeping people witness two different kinds of sleep. The different stages of sleep were discovered through experiments examining the electroencephalogram during sleep. Sleep stages are conventionally scored according to recommendations by a committee chaired by Rechtschaffen and Kales in 1968 [5]. With these rules normal sleep is divided into Rapid Eye Movement (REM) sleep and non-rapid eye movement sleep. Both REM and slow-wave or non-REM sleep stages are indispensable. During slow wave sleep, brain becomes less active, while during REM sleep, the neurons using acetylcholine fire rapidly, producing a dreaming state. Infants sleep up to eighteen hours per day, spending much more time in deep slow wave sleep while older adults may sleep only six to seven hours per night, spending very little time in slow wave sleep. Sleep researchers have found that lack of REM sleep makes human subjects anxious and irritable. Sleeping pills that tend to increase the total sleeping time, but may decrease the time spent in REM sleep, so that when a person stops taking such a drug, several weeks may be required to re-establish the regular sleep patterns. Narcolepsy is a relatively uncommon condition in which one may tend to enter REM sleep as well as a dreaming state of hypnagogic hallucinations very quickly [4]. Currently, sleep recording is usually performed by the polysomnographic technologist in a sleep laboratory.

Brain and neurochemicals in sleep

Sleep-wake cycle is under perfect tuning brought about by the interplay of various neurons of the central nervous system [6]. Neuroimaging studies consider the prefrontal cortex of brain region to be particularly susceptible to the effects of sleep loss [7]. The reticular activating system is a complex neural pathway in our brain that is responsible for maintaining consciousness as well as arousal from deep slumber and is known as 'wakefulness center' [8]. The ascending reticular activating system is located in the caudal midbrain/rostral pontine areas, comprising the serotonergic, noradrenergic and cholinergic neurons. All these neurons together with the histaminergic and orexinergic neurons in the hypothalamus, activate the cerebral cortex through the thalamus or basal forebrain. The mesopontine area also pays a role in the REM sleep regulation. In the REM activating system, mutual excitatory interactions between cholinergic and glutamatergic neurons maintain the REM sleep. The REM activating system in the mesopontine area receives GABAergic inhibitory signals from several neural groups in the periaqueductal gray and the medulla [9]. Thus, the 'thalamo-cerebral cortex unit' adjusts the activation pattern through a top-down action on the subcortical cellular groups acting as the origin of the 'ascending reticular activating system' [10]. Hippocampus-dependent declarative memory benefits particularly from slow-wave sleep, whereas REM sleep benefits procedural memory. The relevant consolidation of hippocampus-dependent memories relies on a crosstalk between the neocortex and hippocampus [11].

Several neurochemicals are known to be involved in slumber [12].

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Acetylcholine is a key neurotransmitter released during arousal and REM, but little during non-REM. Glutamate, a primary excitatory neurotransmitter in the central nervous system and histamine are vital for arousal. Dopamine is believed to contribute to awakening and REM sleep while GABA is widely used during non-REM sleep to slow down neural activity in brain and reduce arousal. Glycine, the main inhibitory neurotransmitter in the spinal cord, is responsible for the paralysis of the muscles of movement during REM sleep. Norepinephrine enhances arousal and serotonin, that was previously thought to be very important for non-REM sleep is now thought to promote wakefulness. Astrocytes of brain are known to play an active role in synapse formation and brain information processing by releasing and up taking glutamate, D-serine, ATP and adenosine. Adenosinergic modulation of the glutamate system has been shown to regulate sleep and adenosine gates both photic glutamatergic and nonphotic input to the circadian clock located in the suprachiasmatic nucleus of the hypothalamus [13]. Orexins or hypocretins are recently discovered excitatory neurotransmitters that promote wakefulness [5]. Orexins, produced from the pre-pro-orexin precursor, are expressed in certain areas of dorsolateral hypothalamus and activate orexin neurons, monoaminergic and cholinergic neurons in the hypothalamus/brainstem regions, to maintain a long wakefulness period. Orexin deficiency even results in narcolepsy in humans, dogs, and rodents, confirming the role of orexin system is maintenance of wakefulness [14-16].

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring indoleamine that plays a pivotal role in regulation of our sleep-wake cycles by causing drowsiness and lowering body temperature. The melatonin secretion coincides with circadian rhythms serving as the 'chemical expression of darkness', characterized by its elevated blood levels during the night [17-21]. Melatonin acting as an 'internal sleep facilitator' has been exploited as an active sleep agent and melatonin receptor agonists are emerging as novel promising treatment options for sleep related disorders .The sleep-promoting therapeutic agents, namely, ramelteon, prolonged-release melatonin and agomelatine, are already in use as an important treatment option for insomnia and transient insomnia [22,23].

Sleep related disorders

Sleep disorders are one of the most common health problems of today's world. It is now well-established that sleep deprivation impairs our cognitive functioning and the total time of REM sleep is increased after stressed condition [24,25]. Insomnia, the first psychosomatic disorder to be described by Johann Heinroth in 1818, is defined as difficulty initiating or maintaining sleep or both and poor quality sleep. The drug-induced insomnia is brought about by anabolic steroids, anti-asthmatic drugs, antidepressants, antiepileptic drugs, antihistamines, anti-muscarinic drugs, anti-obesity drugs, antipsychotic drugs, antiretroviral drugs, metals like arsenic and antimony. According to The International Classification of Sleep Disorders (2005), sleep disorders are classified into eight categories, namely, insomnia, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders, isolated symptoms, and other sleep disorders including sleep-related epilepsy. Most of the major sleep disorders are found to be associated with neurologic problems [26].

Sleep problems including insomnia, apnea and loss of circadian rhythm are associated with various kinds of brain injuries, including neoplasms of the central nervous system in children [27, 28]. Steinert's disease, the most common adult-onset form of muscular dystrophy, is characterised by excessive daytime sleepiness, sleep apneas and REM sleep dysregulation [29,30]. Children with Prader-Willi syndrome, a genetic disorder with hypotonia in infancy, suffer from primary hypersomnia with excessive daytime sleepiness and abnormality of REM sleep rhythm [31,32]. Obstructive sleep apnea, a common sleep disorder, is the repetitive complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. The syndrome is associated with excessive daytime sleepiness or chronic fatigue and is associated with hypertension, stroke and other cardiovascular disorders [33,34]. Mandibular advancement device may provide a therapeutic option for obstructive sleep apnea syndrome. There is a rare and complex sleep disorder, Kleine-Levin syndrome, characterized by recurring periods of excessive sleep and a reduced cognition.

Night work forces individuals to change their normal sleep/wake cycle mounting up their 'sleep debt' and abnormal work schedules are often a source of psychological and emotional distress. Rotating night shift work disrupts circadian rhythms and has been associated with obesity, metabolic syndrome, and glucose dysregulation [35]. A 2007 report by the International Agency for Research on Cancer classified night-shift work as possibly carcinogenic to humans, emphasizing, in particular, its association with breast cancer [36]. Sleep is intimately related to performance and lack of sleep leads to performance deficits in the form of slow cognition, memory impairment, decreased vigilance and attention. Night-time napping strategy may play an effective tool for improving work performance and preventing adverse effects due to night shift work. Acting as anchor sleep, night-time naps suppress increased sleepiness and decreased alertness following awakening from such nap and prevented disturbance of circadian rhythm.

Genetics of sleep-wake cycle

The sleep-wake cycle is under the perfect regulation of the circadian clock [6]. A point mutation in a human clock gene, *Per2* was shown to produce the rare advanced sleep phase syndrome whereas a functional polymorphism in *Per3* was associated with the delayed sleep phase syndrome. A point mutation in the prion protein gene appears to be the cause of fatal familial insomnia while a missense mutation in the gene encoding the GABA-A beta 3 subunit was associated with chronic insomnia. In both animal models and human, a deficiency in the hypocretin system was proposed to be responsible for narcolepsy [37]. *Dec2*, a basic helix–loop–helix protein, is thought to function in the clock as a repressor of *Clock/Bmal1* [38]. Recent study has associated a point mutation in the *Dec2* gene with short sleepers that fall asleep at a normal time, but wake up early so that their average amount of sleep is about 6 hours [39]. The TCR alpha gene (*TCRA*) is an important susceptibility factor for narcolepsy. The mammalian work connecting sleep with learning and memory genes has been largely limited to analysis of BDNF and CREB [12]. The genome-wide association studies have revealed about 14 loci increasing susceptibility to sleep disorders, such as narcolepsy and restless leg syndrome [40]. New technologies that help in integrating genomic, environmental and trait data have excavated the human genes with

known variants causing insomnia, narcolepsy and circadian variation and the list includes Prion Protein Fatal Familial Insomnia (PRNP), hypocretin (HCRT), DQ beta 1 (DQB1) and Period Circadian Protein Homolog (PER2) [41]. The gene-environment interactions are well documented in various sleep disorders, including familial and twin sleep disorders. Most sleep disorders are complex in terms of their genetic susceptibility even within a same family and a single gene mutation based disorders include fatal familial insomnia, familial advanced sleep-phase syndrome, chronic primary insomnia, and narcolepsy with cataplexy [42].

Conclusion

Sleep seems to compensate for wakefulness and is thus homeostatic. Modern uses of communication technology require active interaction that is arousing and therefore counterproductive to accomplishing a relaxed and good quality sleep. Rapid progress in computer technologies has led to the introduction of new high intelligence technologies known as artificial neural networks substituting manual analysis in sleep scoring, aiding in solving of non-linear problems [43]. The field of sleep genetics has also expanded its focus from mammalian model organisms to fruifly, zebrafish and worms, probing queries of sleep circuitry on a molecular level. The identified susceptibility genetic determinants may provide clues to better understanding of the pathogenesis of sleep disorders and to decipher new pharmacological targets. Fairy tales and stories have often mentioned about people like Sleeping Beauty and Rip Van Winkle who sleep for amazingly long periods of time. However, sleep, with its myriad of activities, still remains a mysterious chapter in the book of modern neuroscience.

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