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Physiology, REM Sleep

Joshua Feriante
University of Massachusetts Medical School

Et al.

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Authors

Joshua Feriante[1]; John F. Araujo[2].

Affiliations

[1] University of Massachusetts Medical School
[2] UFRN

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Introduction

Sleep is a reversible state of disconnection from the environment, including reduced consciousness, skeletal muscle mobility, and metabolism.[1][2] All forms of sensory responses are markedly decreased to varying degrees depending on the sleep cycle stage. Although this phenomenon is observed in all species that have been studied and occupies a significant fraction of the human lifespan, the purpose and function of sleep remain poorly understood.[1]

Sleep is measured primarily by polysomnography (PSG) which is considered the gold standard for diagnosing sleep disorders.[1]. PSG reveals that sleep architecture has several distinct stages that vacillate between the non-rapid eye movement (NREM) stages and rapid eye movement (REM) stages.[1][2] The REM stage is of particular interest due to its association with various pathological, psychological, and physiological phenomena. The wide variety of medical and psychiatric pathologies, as well as common pharmacotherapies that can disrupt normal sleep, are summarized in this article. With more than 50 million Americans affected by sleep loss,[3] the treatment of sleep disorders is becoming an increasingly more specialized and interprofessional field with a significant impact on patient health in both acute and chronic settings.

Cellular

The sleep cycle is regulated by the circadian rhythm, a process controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus.[1][4] Circadian rhythms refer to the regulation of physiology and behavior according to the day-night cycle.[3] It acts as a biological clock that influences multiple physiological functions such as body temperature, muscular tonicity, and metabolic activity. This cycle is believed to be maintained by a series of "clock" genes that produce proteins in a 24-hour pattern. The two most commonly studied proteins in mammals are the Clock and Bmal1 proteins that bind together and attach to specific DNA sites of cells throughout the body to activate genes such as Period and Cryptochrome.[3] Upon activation, the genes express proteins that influence a myriad of cellular activities such as signal transduction and metabolism until a negative feedback loop is achieved, inhibiting the Clock-Bmal1 binding to the DNA site. This results in the cyclical wake-sleep pattern that influences a vast array of physiological and behavioral phenomenon dependent upon the time of day.

The SCN receives input from nerve cells in the retina that detect light to regulate the circadian rhythm and sleep via multiple pathways that cause the nocturnal release of ACTH, prolactin, melatonin, and norepinephrine. One of the most commonly recognized pathways by which this occurs is via the stimulation of norepinephrine release by the SCN, which in turn stimulates the pineal gland to release melatonin.[2][4]

Wakefulness is maintained by subcortical structures and pathways activating the cortical system.[2] This system is termed the "ascending arousal system" and utilizes several major neurochemicals, including:

- Norepinephrine (locus ceruleus)
- Serotonin (midline raphe nuclei)

- Histamine (tuberomammillary nucleus)
- Dopamine (ventral periaqueductal gray matter)
- Acetylcholine (pedunculopontine tegmentum and laterodorsal tegmentum of the pons)
- Orexin (perifornical area)

Sleep initiation and maintenance require the successful suppression of the arousal systems via the inhibitory activity of the ventrolateral preoptic (VLPO) area.[2] Such suppressive activity triggers are not well understood, but extracellular adenosine accumulation in the forebrain has been proposed as a possible "sleep switch."[2] Caffeine and theophylline are adenosine receptor antagonists providing further evidence for this hypothesis. The possible involvement of several other molecules is highly likely.

The extraocular movements after which REM sleep is named is largely due to the cholinergic activity of the pedunculopontine tegmentum (PPT) center and glutamatergic activity of the medial pontine reticular formation (mPRF).[5]

Function

The purpose of sleep is not well understood, particularly REM sleep.[1][2][3] Multiple theories regarding sleep function have been proposed, including memory integration and consolidation, neuronal homeostasis, and metabolic conservation. Despite the lack of consensus, the effects of poor sleep, including impaired memory and cognitive function, are well documented.[1]

Mechanism

Sleep exists as two distinct types: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep.[2][3] The hallmark of sleep physiology is the sleep-wake cycle in which a person vacillates between NREM and REM sleep throughout the night. The switches between NREM and REM sleep are controlled by reciprocal inhibition of monoaminergic and cholinergic neurons.[2] Cholinergic neurons become highly active during REM. This increase in cholinergic activity is accompanied by a drastic decrease in adrenergic and serotonergic neuron activity and is reversed in NREM sleep. This results in a series of distinct stages of differing wakefulness levels that characterize the different stages of normal sleep.

Sleep architecture is influenced by two separate processes: process S and process C.[4][3] Process S is also called the "homeostatic sleep drive" and increases activity with each hour spent awake. Process C refers to the circadian rhythm and is responsible for maintaining appropriate sleep/wake cycles by promoting sleep during the night and wakefulness during the day. This drive increases throughout the day until bedtime when it begins to decline to promote sleep consolidation.

Related Testing

Two modes of measurement exist in sleep physiology: behavioral assessment and physiological monitoring.[2] Behavioral monitoring of sleep includes observing the loss of consciousness, eye closure, and the increase of skeletal muscle hypotonia as NREM sleep progresses to REM sleep. In addition to clinical observation, the quality of sleep can be reported by the patient subjectively assessing the maintenance of sleep and the degree to which the patient feels refreshed upon waking and during the day.

The gold standard of physiological monitoring is the polysomnogram (PSG).[2] The polysomnogram is performed by attaching noninvasive sensors to the patient to record brain activity via electroencephalogram (EEG), eye movement, submental muscle tone, leg movements, and cardiac activity with an electrocardiogram. Oral and nasal airflow sensors, finger oximeters, and thoracic and abdominal strain gauges are also utilized to monitor respiratory activity during sleep. PSG is used to identify the 3 stages of NREM sleep (N1-N3), and REM sleep by measuring specific EEG waveform rhythms and events[6] outlined briefly below:

- Alert wakefulness: low-amplitude mixed frequency EEG
- Drowsy wakefulness: alpha waves with 8 to 13 Hz peaks
- N1 stage: 4 to 7 Hz Theta waves (sawtooth)
- N2 stage: 11 to 16 Hz spindles (bursts of waves) and 0.5 to 2 Hz K-complexes (biphasic waves)
- N3 stage: 0.5 to 3 Hz Delta waves (large and slow)
- REM sleep (stage R): theta waves or wave-like patterns

The onset of sleep begins with wakefulness and progresses rapidly to REM sleep by approximately 60 to 90 minutes.[2][6] This is followed by cyclical alterations between REM and NREM every 90 to 120 minutes until awakening. Most REM sleep occurs during the second half of the night, with NREM sleep dominating the first half of the night.

A variety of parameters are used to measure REM sleep, including the time to onset, length of the REM stage, and amount of eye movement that occurs during REM.[6] REM latency refers to the amount of time elapsed between the onset of sleep to the first REM stage. REM density refers to the number of eye movements during REM sleep, and changes have been associated with sleep deprivation and depression.

Pathophysiology

There are a wide variety of pathologies that interrupt normal sleep physiology. A few of the most common are included below:

Physiological Disruptions of Sleep

Narcolepsy results from the inherited loss of orexin-releasing neurons in the lateral hippocampus, which causes somnolence, sleep cycle disruptions, and cataplexy.[2][7] A hallmark feature of narcolepsy is episodes of uncontrollable sleepiness that results in waking refreshed, referred to as “sleep attacks.” This is due to aberrant activation of REM sleep circuits that result in the paralysis or hypotonia characteristic of narcolepsy.[7] Cataplexy is pathognomic for this condition and consists of loss of muscle tone that is often induced by stressors such as loud noises or heightened emotions. Hypnagogic (upon going to sleep) and hypnopompic (upon waking) hallucinations are more common in narcoleptics than the general patient population, as is sleep paralysis (most common upon waking).

Obstructive sleep apnea (OSA) is the cessation of airflow despite normal respiratory effort due to partial or complete obstruction of the upper airway.[8][6] Polysomnography is the gold standard test to diagnose OSA. REM sleep correlates with the severity of sleep apnea secondary to the differences in sleep positions between REM and NREM sleep.[8] In particular, apneic episodes can be observed with PSG and are more prevalent during REM sleep due to the prevalence of patients sleeping in the supine position. This is associated with an increased frequency of apneic episodes with no effect on the duration of episodes.

Psychiatric Disruptions of Sleep

Major depressive disorder (MDD) has been associated with decreases in REM latency, increased REM density, and a prolonged first REM cycle.[6] Multiple studies have shown that antidepressants (including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants) and cognitive behavioral therapy both serve to normalize sleep architecture. Nearly all antidepressants cause increased REM latency and reduce total REM sleep time. Interestingly, shortened REM latency persists during remission and is even present in patients with a strong family history of depression who do not present with symptoms of MDD

Bipolar disorder (BD) is characterized by the broad range of sleep disturbances that are observed as a patient fluctuates between episodes of mania, bipolar depression, and euthymia.[6] REM latency is shorter, and REM density increased in both manic and depressed episodes. Euthymic BD patients experience similarly shortened REM latencies

yet experience increased total REM sleep. Of note are the positive correlations between the duration of the first REM period with manic symptoms and REM density with depressive symptoms that last greater than three months.

Schizophrenia is associated with several changes in REM sleep, including reduced REM latency, higher REM density, and the failure to rebound from REM sleep deprivation.[6] These changes have not been proven to be consistent, however. Appropriate treatment with antipsychotics has been associated with increased total sleep time and REM latency. Several differences exist between typical and atypical antipsychotics, which suggests that the second-generation antipsychotics have additional beneficial effects on sleep via management of other psychiatric symptoms such as depression and cognitive impairment.

Parasomnias are a class of pathologies defined as behavioral manifestations of partial arousals from sleep, particularly REM sleep.[9] Parasomnias can present with physiological abnormalities during the REM stage, including impaired or painful sleep-related erections, bradycardia, and cardiac sinus-arrest. Other parasomnias include phenomena associated with REM sleep, such as dreaming and can manifest as nightmare disorder. Other disorders involve the aberrations of REM-related muscle atonia, which results in behavioral disorders such as recurrent isolated sleep paralysis and REM behavior disorder.

REM behavior disorder (REMBD) is a particularly interesting parasomnia. REMBD is an idiopathic disturbance of sleep architecture characterized by significantly decreased REM muscle atonia that results in the active enactment of dreams during REM sleep.[10][6] REMBD is found in approximately 0.5% of the elderly population and has a strong association with parkinsonian syndromes such as Lewy body dementia (LBD), Parkinson disease (PD), and multiple system atrophy (MSA).[3][10][6] In fact, several studies have shown that the majority of patients who experience REMBD are subsequently diagnosed with one or more of these syndromes.

Insomnia is characterized by the dysfunction of sleep onset or maintenance not caused by substances or secondary medical conditions.[11] Studies have shown that insomnia is associated with decreased total REM sleep and slow-wave sleep. Sedative-hypnotics that promote GABA signaling, such as zolpidem or triazolam, are the first-line treatment for patients experiencing sleep-onset type insomnia, although 5-HT2 inhibitors are recently being developed as potential treatments for insomnia.[4]

Several common substances and medications are associated with REM sleep disruption. Alcohol is a commonly used substance for self-medication and significantly delays the first onset of REM sleep.[12]

Clinical Significance

Over 50 million Americans suffer from sleep loss, which is defined as a sleep duration less than the average of 7 to 8 hours per night.[3] Acute and chronic sleep loss results in a wide variety of detrimental consequences. Acute sleep loss results in several deleterious symptoms, including daytime somnolence, diminished memory, and hampered concentration. Chronic sleep loss has been consistently associated with an increased risk of serious diseases, including diabetes, obesity, and depression. Moreover, sleep deprivation is associated with significantly increased cardiovascular disease, including hypertension, heart attack, and stroke.[3] Sleep disorders are readily treatable and are an important factor in the comprehensive care of patients.

Continuing Education / Review Questions

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