

# Mechanisms of Sleep-Wake Cycle and Genetics of Sleep Disorders. A Review.

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## Abstract

Sleep is indispensable to replenish energy sources in the brain that are depleted during wakefulness. A variety of significant physiological changes occur in all body systems and organs during sleep as a result of functional alterations in the autonomic and somatic nervous systems. Inadequate sleep and sleep disorders have important adverse consequences on multiple systems with particular relevance to cardiovascular disease such as high BP, insulin resistance, systemic inflammation, visceral fat deposition and Parkinson's disease.

**Key words:** Sleep, restless leg syndrome, narcolepsy, hypocretin, adenosine.

## 1. Introduction

Normal sleep consists of alternation between REM and NREM stages. Characterized by the presence of synchronized waves in the EEG, NREM sleep can be subdivided into four phases (phases 3 and 4 correspond to slow-wave sleep or delta sleep). The REM sleep stage is characterized by EEG desynchronization and low-amplitude waves [1].

The release of several different neurotransmitters from the brain stem, hypothalamus, basal forebrain, and cerebral cortex results in a depolarization of thalamocortical and thalamic reticular neurons and an enhanced excitability in many cortical pyramidal cells, thereby suppressing the generation of sleep rhythms and promoting a state that is conducive to sensory processing and cognition [2].

## 2. Sleep-wake cycle mechanisms

### 2.1. Cholinergic and monoaminergic systems

The synchronization-desynchronization of EEG waves during NREM-REM sleep and wakefulness is a consequence of neural activity in the thalamocortical circuits (reticular nuclei in the thalamus and cerebral cortex), derived from the interaction between monoaminergic and cholinergic nuclei in the brain stem [3].

The monoaminergic system of ascending reticular activation is composed of the serotonergic dorsal raphe nuclei (DRN), noradrenergic locus coeruleus (LC) of the brain stem and the histaminergic tuberomammillary nucleus (TMN) in the posterior hypothalamus, which diffusely projected to the cortex and reticular nuclei of the thalamus [1].

The thalamocortical circuit and the aminergic-cholinergic projections are responsible for the desynchronization of the EEG during wakefulness. High aminergic activity during active wakefulness activates the thalamocortical circuits but is reduced during NREM sleep, and is absent during REM sleep. Aminergic neurons are called wake-on-and-sleep-off cells. Cerebral cortex is aminergically demodulated during REM sleep due to the lack of hypocretin tone [4].

Cholinergic thalamocortical and limbic thalamocortical projections are fundamental for desynchronization of the EEG during wakefulness and during REM sleep. In contrast with aminergic activity, which is absent during REM sleep, the cholinergic activity of the dorsolateral pontine and pedunclopontine tegmental nuclei, as well as that in the nucleus basalis of the forebrain, is at a maximum during REM sleep and wakefulness but is minimal or absent during NREM sleep [1] [3].

Therefore, cholinergic nuclei are activated during wakefulness and during REM sleep with EEG desynchronization. Cholinergic cells are known as "REM-and-wake-on" cells [1] [3]. During wakefulness, aminergic, dopaminergic, hypocretin and cholinergic systems are active (cortical aminergic modulation) [5].

### 2.2. Dopaminergic mechanisms of sleep regulation

Neurons in the mesencephalic VTA, situated next to the substantia nigra, project to the cerebral cortex via the mesocortical limbic pathway. Excitatory axons of the VTA are projected to the LC and the limbic thalamic nuclei, connecting the mesostriatal dopaminergic system directly with the ascending activating system responsible for wakefulness [3]. Neurons in the mesencephalic ventral tegmental area receive excitatory synapses from hypocretinergic cells in the lateral hypothalamus which, together with the excitatory activity of aminergic, cholinergic and hypocretin systems, promote EEG desynchronization during wakefulness [1] [3].

Galaninergic and GABAergic inhibitory neurons of the VLPO of the anterior hypothalamus are exclusively activated during NREM and REM sleep (sleep-on). The VLPO is related to slow-wave sleep, Cells are directly projected from the VLPO to the TMN, DRN, LC, cholinergic dorsolateral pontine and pedunculopontine tegmental nuclei, as well as to the hypocretin system, inhibiting the wake-promoting excitatory effect of these nuclei [4].

The VLPO remains active, inhibiting the hypocretin, aminergic and cholinergic systems and, since it inhibits REM-off cells, allows REM sleep to begin. The VLPO receives inhibitory synapses from the TMN, DRN and LC, as well as from the limbic system nuclei and suprachiasmatic nuclei (SCN). Therefore, the VLPO and the aminergic system have a functional relationship of reciprocal inhibition [3] [4]. When the VLPO is active during sleep, it inhibits cells in the aminergic-cholinergic system. Likewise, when the aminergic-cholinergic neurons are active during wakefulness, they inhibit the VLPO [1].

### 2.3. Homeostatic control of sleep – adenosine

In the CNS, ATP signaling can regulate both excitatory and inhibitory neurotransmission. Many neurons can release ATP in an activity-dependent manner, and this molecule can act as a potent neuromodulator for neuron–neuron and neuron–glial signaling. ATP and its metabolites regulate multiple processes in the nervous system including sleep regulation [6].

Adenosine product of neuronal energy metabolism at the cellular level, accumulates in the synaptic cleft during wakefulness and acts as a local inhibitor. Cells in the basal forebrain are with largest local accumulation of adenosine during wakefulness and sleep deprivation. Therefore, the basal forebrain is considered the homeostatic regulator of sleep [7]

The local inhibitory action of adenosine occurs in specific adenosine-1 autoreceptors of cholinergic cells in the basal forebrain. The decrease in the activity of these cholinergic cells blocks inhibition of GABAergic cells in the VLPO as well as blocking stimulation of the hypocretin system, initiating NREM sleep at the end of the period of activity or wakefulness [1].

The reduction in cholinergic activity in the basal forebrain caused by the accumulation of adenosine blocks inhibition of the VLPO, which, in conjunction with the SCN effect, induces NREM sleep. This is the double trigger for sleep onset [3].

ATP levels drastically change during sleep in several brain regions and are directly related to SWA in NREM sleep. And, sleep deprivation for 3 h induces a significant reduction in ATP concentration in the frontal cortex and lateral hypothalamus (an area known to predominantly contain wake- and REM-active neurons) although sleep deprivation does not affect the VLPO, an area known to predominantly contain sleep-active neurons [6]. Infusion of adenosine and adenosine transport inhibitors into the basal forebrain increases sleep in cats and rats [8].

### 3. Genetics of sleep and its disorders

Gene variants conferring risk for sleep disorders can be classified into three broad categories

1. Common variants with small effects. The minor allele frequency is >5%. The increment in risk from these variants is small, typically 1.1–1.5-fold.
2. Rare variants with large effects. These may or may not cause classical Mendelian disease. In this class are variants with a minor allele frequency of <0.05%. They can have substantial effects, e.g., increasing disease risk by three-fold or more
3. In between these extremes are variants with low minor allele frequency, i.e., between 0.5% and 5% [9].

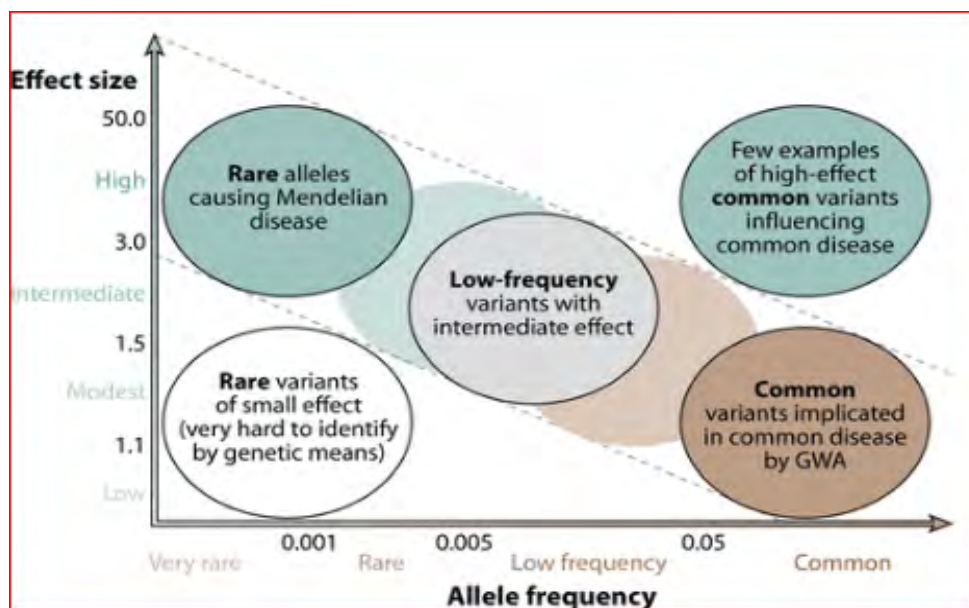


Figure 1. Types of Gene Variants Conferring Risk for Disease.

The Y axis is the magnitude of the effect of the variant in terms of odds ratios. The X axis is the minor allele frequency. To the left of the diagram are rare variants with large effects. To the right are common variants with small effects. These are identified by genome-wide association studies. In between are variants with intermediate frequency and intermediate effect [9]

### 3.1 Restless legs syndrome

Restless legs syndrome (RLS) (Ekbom's syndrome) is a sensorimotor disorder characterized by an irresistible urge to move the limbs accompanied by uncomfortable sensations, leading to sleep disturbances [10].

There are four features: (a) unpleasant sensations in the legs that are associated with an urge to move; (b) worsening of the symptoms by rest; (c) lessening or relief of symptoms by movement; and (d) diurnal variation in the intensity of the symptoms, with worsening of the symptoms in the evening and at night. It is this last feature that leads to difficulty with sleep. There is a marked difference in prevalence in different countries and ethnic groups [11].

#### 3.1.1 Clinical description

RLS is characterized by an internal urge to move the limbs during times of rest, with relief of discomfort brought about by movement. Accompanying sensory symptoms may be described as tingling, crawling, burning, grabbing, pain, throbbing, "itching bones," and "soda bubbling in the veins." [12]. Even though the legs are most commonly involved, RLS symptoms involve the arms and, rarely, the axial muscles [13]. Patients will pace the floor, rub their legs against each other, apply hot or cold packs to their legs, or stretch in order to relieve symptoms. Patients often report difficulties in air travel, riding a car, or sitting in theater for prolonged periods of time [12].

Sleep disturbance is prominent in RLS [14]. There is significant decrease in total sleep time and sleep efficacy, and increase in nocturnal awakenings. Fine motor activity and reaction time performance was also significantly less in RLS patients. Daytime EEG mapping of the RLS patients compared with controls, RLS patients had significantly increased delta and fast alpha power and decreased slow alpha power [10].

#### 3.1.2. Periodic limb movements

PLMs are involuntary movements involving flexion at the hip, knee, and ankle. Periodic limb movements of sleep (PLMS) are nocturnal PLMs and are defined electromyographically as a sequence of  $\geq 4$  muscle contractions occurring during sleep at 5–90 second intervals and lasting 0.5–5.0 seconds. Whereas the symptoms of RLS include a subjective uncomfortable sensation in the limbs that leads to voluntary, albeit irresistible, limb movement, PLMS are involuntary and can be objectively diagnosed by electromyography [10].

The prevalence of PLMS is high among RLS patients; and ~80% of RLS patients meet the diagnostic criteria for PLMD. However, only ~30% of patients with diagnosed periodic limb movement disorder (PLMD) have symptoms of RLS and RLS can occur entirely without features of PLMD in up to one out of five patients [15], [16].

### 3.1.3. RLS and its effects on daily life activity

Patients with chronic sleep disorders are more prone to depression [20] and RLS patients have shown higher rates of anxiety and depression [10]. Among 917 patients presenting to a sleep disorders clinic, it was found that patients with PLMD/RLS had a  $\geq 50\%$  chance of having some form of depression [17]

The most profound deficits were related to vitality/energy and limitations of work and activities due to physical problems [10]. The impact of RLS on quality of life was found to be equal to or greater than that of patients with other major chronic medical conditions, including chronic obstructive pulmonary disease and myocardial infarction [18].

### 3.1.4. Genetics of restless legs syndrome

Familial RLS exhibits age-dependent penetrance, with 56% penetrance to the age of 40 years and full penetrance by 60 years of age and variable expressivity. RLS also shows anticipation [19].

There is linkage for a locus on chromosome 9 [20]. There is also a “difference in the mode of inheritance of RLS between families with an early versus a late age at onset.” Families in whom mean age of onset was  $\leq 30$  years of age showed an autosomal-dominant mode of inheritance, whereas families showing a later mean age of onset did not follow a clear-cut mode of inheritance [10][21].

## 3.2 RLS and Other Associated factors

### 3.2.1. Iron deficiency and RLS

Iron deficiency is an established cause of RLS, and Iron therapy resolves symptoms in many cases [22]. Serum ferritin levels have been found to correlate best with RLS symptoms and severity and decreased ferritin levels in the absence of overt anemia have been shown to be associated with RLS [23]. Three general explanations have been used to describe the development of the syndrome: (1) an abnormal subcortical functioning in the substantia-nigra of the brain, where the localization of the disorder exists in the central nervous system (2) inadequate dopamine metabolism in the brain (3) inadequate iron metabolism in the brain [24].

Up to 23% of pregnant women experience RLS and RLS during pregnancy is a risk factor for later development of the disease. The risk of RLS increases with the number of births [10].

### 3.2.2. RLS and diabetes

One sleep disorder that may affect the management of diabetes is restless legs syndrome, 21% of persons with RLS have diabetes, a prevalence more than 3 times that of the general population. In Brazil, RLS was found in 27% of people with diabetes [24]. Diabetes has been suggested to be a cause of RLS [10]. Restless legs syndrome may compromise glycemic control because of associated consequences of sleep deprivation, fatigue, and depression [24].

### 3.2.3. RLS and Parkinson's disease

There is association of RLS and Parkinson's disease, of 126 Parkinson's disease patients 7.9% suffer from RLS compared with only 0.8% of controls [25]. Another study of 303 patients with Parkinson's disease found 20.8% to have RLS [26].

## 4. Narcolepsy

Narcolepsy is a disorder characterized by high pressure for rapid-eye movement (REM) sleep [9]. Narcolepsy is debilitating lifelong rapid eye movement (REM) sleep disorder, characterized by the classic tetrad of excessive daytime sleepiness with irresistible sleep attacks, cataplexy (sudden bilateral loss of muscle tone), hypnagogic hallucination, and sleep paralysis [27].

Other features include fragmented night sleep and automatic behavior, loss of concentration and memory, and blurry vision. The presentation is variable in terms of symptoms and intensity over time, and only about 10% of patients concurrently exhibit all components of the tetrad [27].

### 4.1. Genetic and environmental basis

Most cases of narcolepsy are sporadic, but there are definite cases with familial clustering [27]. The risk of narcolepsy in first-degree relatives of patients is 10–40 times higher than in the general population. There is an environmental contribution as well, as shown by reported concordance rates of 25%–31% in monozygotic twins. The onset is associated with nonspecific environmental factors, such as head trauma, stroke, and change in sleep-wake cycle. There is an association with streptococcal infection, H1N1 vaccination or infection, and exposure to heavy metals, insecticides, and weed killers [28], [29].

#### 4.1.1. HLA haplotype

More than 85% of patients having narcolepsy with cataplexy have HLA DQB1\*0602, often in combination with HLA DR2 (DRB1\*1501), while only half of patients having atypical, mild, or narcolepsy without cataplexy have HLA DQB1\*0602. Other alleles of HLA also affect the predisposition to narcolepsy with cataplexy [30].

#### 4.1.2. Hypocretins

Hypocretins 1 and 2, (orexins A and B) the two dorsolateral hypothalamic neuropeptides function in regulating sleep-wake cycles, food intake, and pleasure-seeking behavior. The areas of the brain that the neurons producing hypocretins project to are the locus ceruleus, tuberomammillary nucleus, raphe nucleus, and ventral tegmental areas. These areas correspond to norepinephrine, histamine, serotonin, and dopamine secretion, respectively. Deficiency of hypocretin could lead to malfunctioning of these systems and therefore abnormalities of REM sleep and excessive daytime sleepiness [31].

Dopamine has significant wakefulness promoting properties, as does histamine. Abnormalities related to rapid eye movement (REM) sleep can be produced with the changes to the adrenergic and serotonergic systems [32].

Study of Doberman Pinschers shows the presence of fragmented sleep, episodes similar to cataplexy, and short REM sleep latencies. Genetic analysis shows a dysfunctional receptor in the neuropeptide system, specifically hypocretin 2 receptor. Hypocretin 2 receptor knockout mice display episodes similar to cataplexy. Animals, without the hypocretin 1 receptor are not observed to have cataplexy-like behaviours, but do show fragmentation of their sleep [29] [32].

Human pathology studies have revealed reductions of *Hcrt1*, *Hcrt2*, and *preproHcrt* mRNA. The resultant low level of hypocretin despite normal *Hcrt* genes lends to the idea that narcolepsy is the result of an autoimmune process. Narcolepsy has a typical onset in the second and third decades of life, which is common in many other autoimmune disorders [32].

Unlike in animals, hypocretin deficiency in humans having narcolepsy with cataplexy was not due to mutation in hypocretin genes but rather secondary to loss of hypocretin neurons in the dorsolateral hypothalamus [24].

#### 4.1.3. Autoimmunity

The combination of HLA antigens, hypocretin deficiency, hypocretin neuron loss, the rarity of hypocretin gene mutations, and onset in the second decade of life points strongly towards an autoimmune etiology [27], there are autoantibodies against *Trib2* in 26.1% of patients having narcolepsy with cataplexy compared with 2.3% of healthy controls. Thus, a subgroup of patients having narcolepsy with cataplexy might be suffering from anti-*Trib2* autoimmune disorder [33], and higher interleukin-6, tumor necrosis factor- $\alpha$ , tumor necrosis factor receptor p75 levels in patients having narcolepsy with cataplexy [27].

### 5. Conclusion

This review outlines an overview of sleep wake cycle mechanisms and genetic and environmental basis of sleep disorders and their effect on person's daily life. It is evident that the recent rise in the sleep disorders due to stressful working environments and night shift working times may affect persons of differing age groups, of both genders. Sleep disorders were also significantly correlated to other comorbid factors like obesity so in the future the exact pathophysiologic mechanisms should be meticulously explored and the causal relationship should be thoroughly examined to improve the lives of patients with sleep disorders by designing special treatment modalities which include treatment of sleep disorders in addition to treating the underlying diseases.

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