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Control of sleep in mammals

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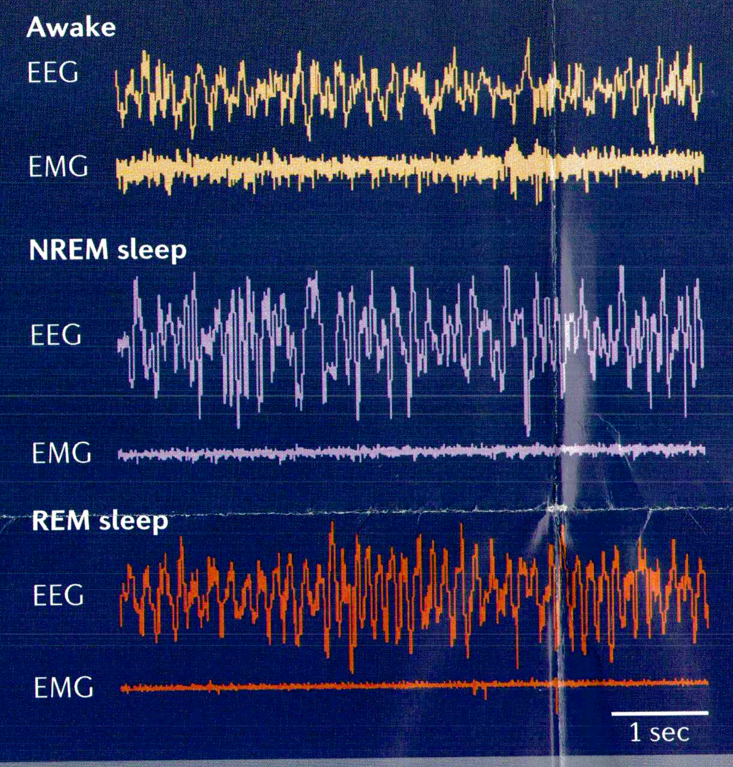
The onset of mammalian sleep is associated with an increase in the activity of sleep-active neurons and a decrease in the activity of wake-active neurons. In most mammals, including humans, sleep consists of rapid eye movement (REM) and non-REM (NREM) phases. Studies, most of which have been conducted in rodents or cats, show that neurons that are active during NREM sleep are scattered in groups between the basal forebrain and the medulla. By contrast, the pons, a major site of REM-active neurons, is sufficient for the generation of REM sleep. The suprachiasmatic nucleus (SCN) regulates sleep tendency over the 24-hour period. Here, we provide an overview of the current understanding of sleep generation, pathology and function.

Sleep basics

Sleep comprises two distinct states: REM sleep and NREM sleep. When going to sleep, individuals usually enter the NREM state, which is characterized by high-voltage cortical slow waves (as observed on EEGs), slow but regular respiration rate and heart rate, and a reduction in muscle tone (as observed on EMGs) compared with waking levels. The REM sleep state usually follows NREM sleep and is characterized by low-voltage cortical waves that resemble those observed in the awake state in humans, cats and dogs. In rodents, prominent cortical theta waves (4–8 Hz) occur during REM sleep. REM sleep is also characterized by irregular respiration and heart rate, penile erections and clitoral engorgement, rapid eye movements and, paradoxically, minimal muscle tone. The NREM and REM states alternate throughout sleep, and individuals can experience awakenings from either state. Direct transitions from waking to REM sleep are generally seen only in pathological conditions such as narcolepsy. The displayed traces come from mice.

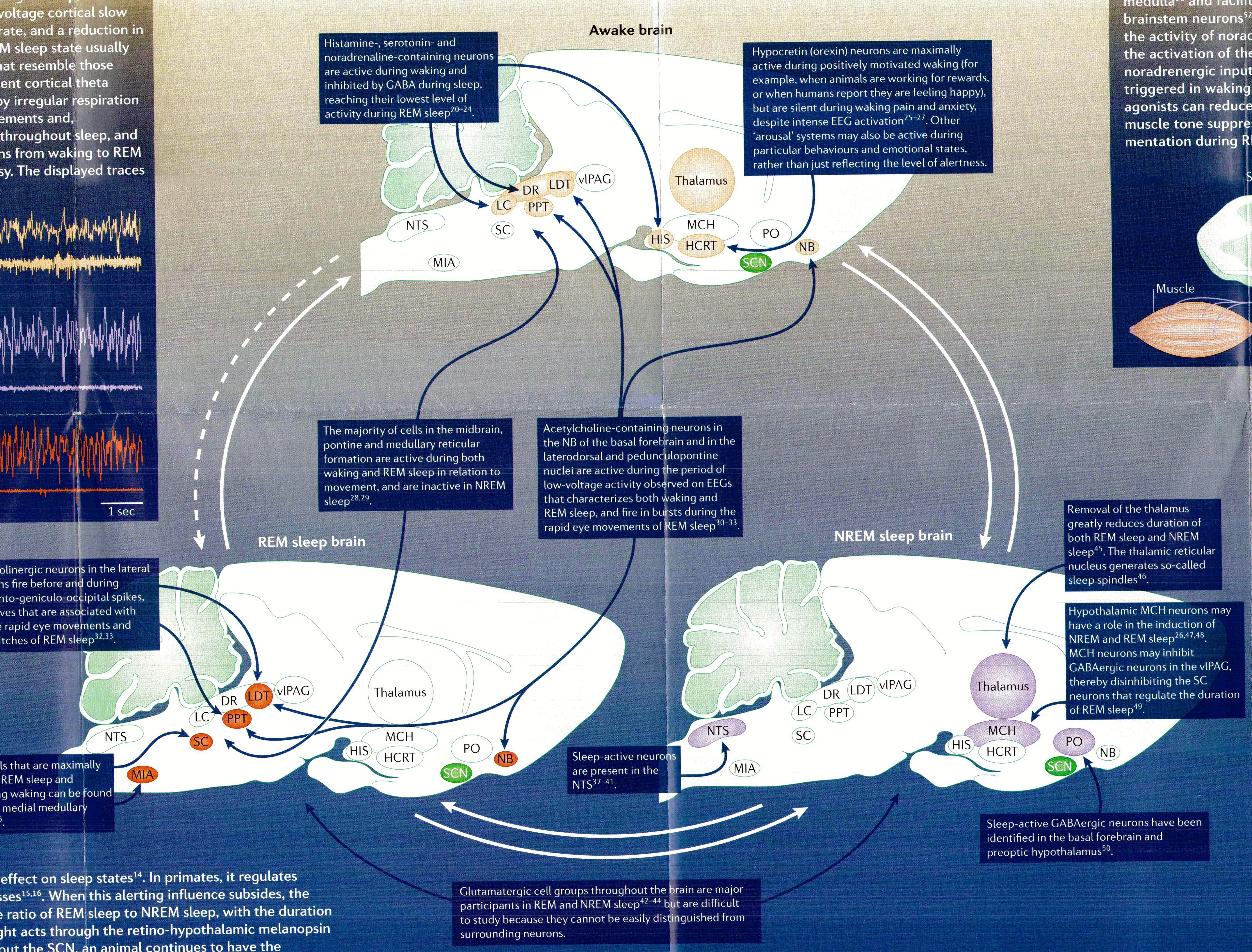
The amount of time spent awake versus asleep is under circadian regulation (see below) and homeostatic regulation. The neural mechanisms of homeostatic control remain unclear, although adenosine has been implicated in the control of NREM sleep[1–3], accounting for the activating effects of the adenosine receptor antagonist caffeine. The interaction between the circadian and homeostatic mechanisms has been modelled by Borbely[4]. Deprivation of sleep or REM sleep results in a 'rebound' of the deprived states after the period of deprivation. The amount of lost sleep is not usually recovered, but the recovery sleep can be considered to be more 'intense', with higher-voltage slow waves during NREM sleep and more rapid eye movements and twitching during REM sleep.



Why we sleep

There is little agreement on the functional role of sleep states, with synaptic sculpturing and homeostasis[5,6], brain metabolite clearance[7] and immune function[8] being recent hypotheses of sleep function. Daily sleep duration varies tremendously across mammalian species, ranging from 2 to 20 hours. Sleep duration is not strongly correlated with brain size or the brain weight–body weight ratio across species, but is associated with species-specific diet: herbivores sleep the least, omnivores sleep more and carnivores sleep the most[9]. This pattern is consistent with sleep having an adaptive role in acquiring food and conserving energy. Sleep parameters in humans are not correlated with learning ability[10,11] or intelligence quotient[12,13].

The sleep cycle and neural correlates of sleep and awake states

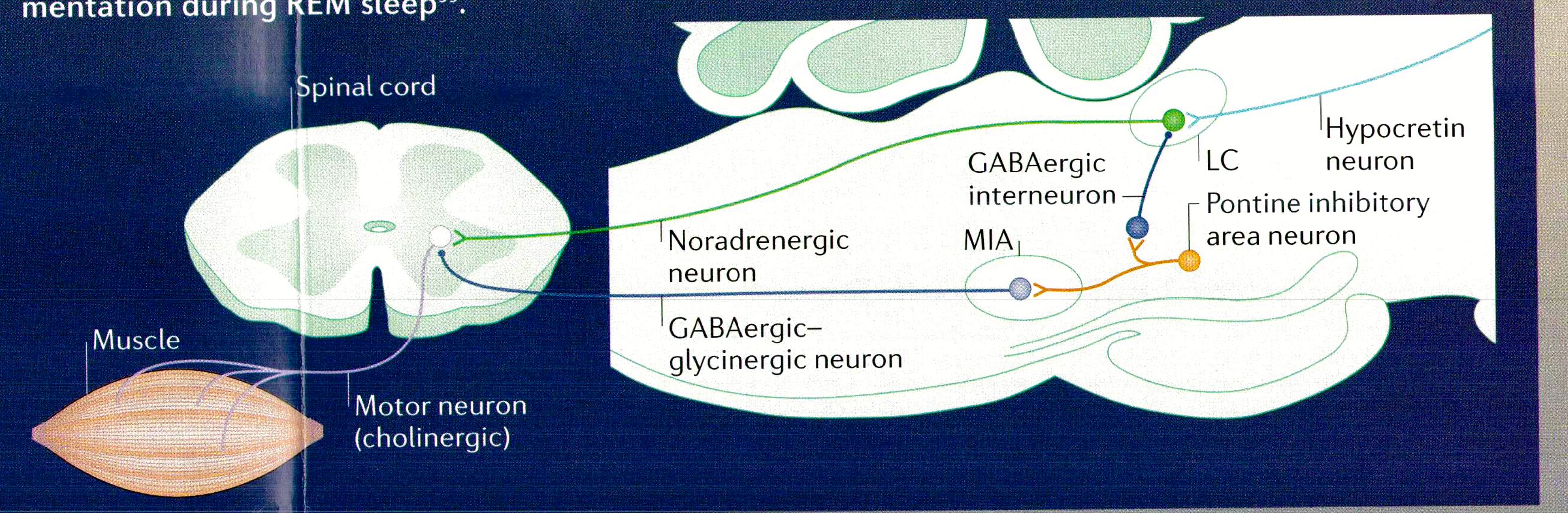


Circadian control of sleep

The SCN is the major synchronizer of 24-hour rhythms and has a potent effect on sleep states[14]. In primates, it regulates a circadian alerting signal that counteracts sleepiness as the day progresses[15,16]. When this alerting influence subsides, the NREM–REM sleep cycle is initiated. The circadian rhythm also affects the ratio of REM sleep to NREM sleep, with the duration and intensity of REM sleep periods increasing at the end of the night. Light acts through the retino-hypothalamic melanopsin system to entrain the circadian rhythm to the solar day[17]. However, without the SCN, an animal continues to have the expected amount of NREM sleep and REM sleep, indicating that the SCN is not essential for the production of these states[18,19].

Loss of muscle tone during REM sleep

Motor neurons receive projections from a GABA–glycine motor-inhibitory system in the medial medulla[51] and facilitation from the noradrenergic neurons in the LC and from other noradrenergic brainstem neurons[52,53]. During waking, a caudal projection from hypocretin cells to the LC maintains the activity of noradrenergic cells[52,54–57]. During REM sleep, muscle tone is reduced or eliminated by the activation of the GABA–glycine input on to motor neurons and simultaneous inactivation of the noradrenergic input, under the control of the pons[58]. This same pattern can be pathologically triggered in waking in individuals with narcolepsy, resulting in cataplexy[51–53]. Noradrenergic agonists can reduce cataplexy in individuals with narcolepsy. In REM sleep behaviour disorder, this muscle tone suppression system does not get fully activated, resulting in an 'acting out' of dream mentation during REM sleep[59].



Sleep pathologies

Disorder	Clinical features	Underlying deficit	First-line treatment
Insomnia[60]	Inability to fall asleep or maintain sleep; feelings of inadequate sleep (even after non-shortened sleep)	Unknown in most cases; rarely, brain lesions; can occur with hyperarousal, depression or PTSD	Cognitive behavioural therapy
Sleep apnea[61]	Interrupted, obstructed breathing, causing hypoxia	Small-diameter airway and reduced tone in airway muscles, leading to airway collapse during sleep	Continuous positive airway pressure, delivered through a mask
REM sleep behaviour disorder[59]	Acting out dreams; injury during sleep	Damage to motor suppression regions in brainstem	Clonazepam
Periodic leg movement disorder; often seen in combination with 'restless legs' syndrome[62]	Regular twitches, usually of the legs	Unknown; potentially a brainstem abnormality	Dopamine agonists
Narcolepsy[63]	Sleepiness; cataplexy; hallucinations at sleep onset and offset; sleep paralysis	Loss of hypocretin neurons[55,56]; a greatly increased number of histaminergic neurons[64,65]	Stimulants to counteract sleepiness; antidepressants or noradrenergic agonists to prevent cataplexy; sodium oxybate for both symptoms

Abbreviations

DR, dorsal raphe
EEG, electroencephalogram
EMG, electromyograph
HCRT, hypocretin
HIS, histamine
LC, locus coeruleus
LDT, laterodorsal tegmental nucleus
MCH, melanin-concentrating hormone
MIA, medullary inhibitory area
NB, nucleus basalis
NREM, non-rapid eye movement
NTS, nucleus of the solitary tract
PO, preoptic hypothalamus
PPT, pedunculopontine tegmental nucleus
PTSD, post-traumatic stress disorder
REM, rapid eye movement
SC, subcoeruleus
SCN, suprachiasmatic nucleus
vlPAG, ventrolateral periaqueductal grey

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Competing interests statement

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