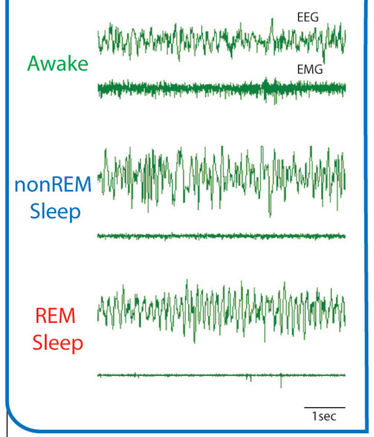
Control of sleep in mammals

Ronald McGregor and Jerome Siegel

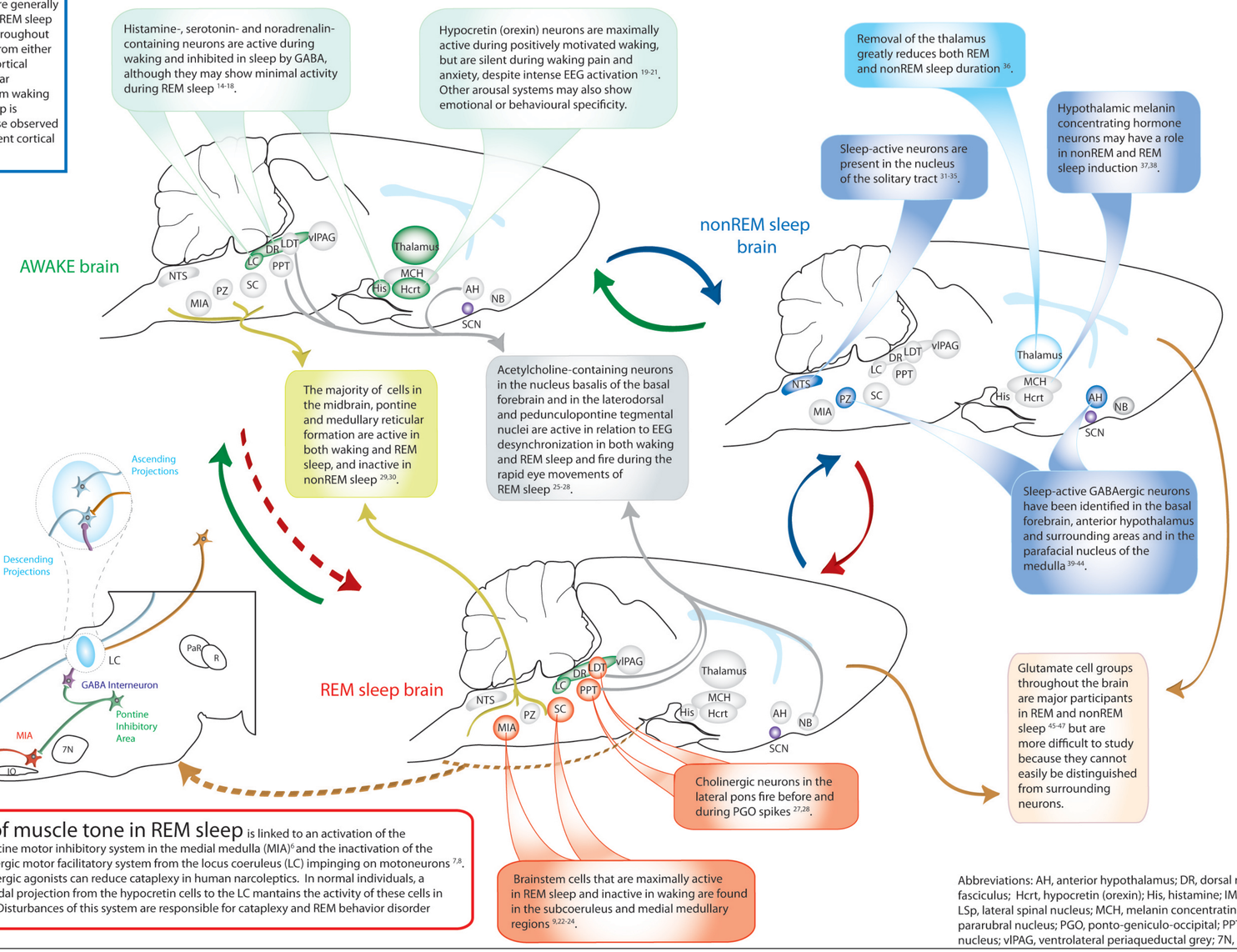
Sleep in most mammals, including humans, consists of rapid eye movement (REM) and nonREM phases. Deprivation of sleep per se or of REM sleep results in a "rebound" of the deprived states, but the amount lost is not completely recovered. Studies, mostly conducted in rodents and cats, show that neurons that are active during non REM sleep are scattered in groups from the basal forebrain to the medulla. By contrast, the pons contains neurons that are active during REM sleep and indeed this area is sufficient for REM sleep generation [5].

Sleep Basics

Normal human sleep is comprised of two distinct states: REM and nonREM sleep. When going to sleep, individuals usually enter the NonREM state; direct transitions from waking to REM sleep are generally seen only under pathological conditions such as narcolepsy. REM sleep usually follows nonREM sleep and the two states alternate throughout the period of sleep. Individuals can experience awakenings from either state. NonREM in humans is characterized by high-voltage cortical waves (as seen on electroencephalograms, EEGs), slow, regular respiration and heart rate and a reduction in muscle tone from waking levels (as seen in electromyographs, EMGs). Human REM sleep is characterized by low-voltage cortical waves, resembling those observed during waking in humans, cats and dogs. In rodents, prominent cortical theta (4-8 Hz) waves are seen in REM sleep. REM sleep in all mammals is characterized by irregular respiration and heart rate, REMs, and paradoxically, by minimal muscle tone. The traces below show EEG and EMG data from a rodent.



Sleep cycle and neural correlates of the different sleep-wake states



Loss of muscle tone in REM sleep is linked to an activation of the GABA/glycine motor inhibitory system in the medial medulla (MIA)[6] and the inactivation of the noradrenergic motor facilitatory system from the locus coeruleus (LC) impinging on motoneurons [7,8]. Noradrenergic agonists can reduce cataplexy in human narcoleptics. In normal individuals, a major caudal projection from the hypocretin cells to the LC mantains the activity of these cells in waking [9]. Disturbances of this system are responsible for cataplexy and REM behavior disorder

Circadian control of sleep

The suprachiasmatic nucleus (SCN), which is the major synchronizer of 24h rhythms in mammals, has a potent effect on sleep states[10]. In humans, the SCN regulates a circadian alerting signal that counteracts sleepiness as the day progresses [11,12]. When this alerting influence subsides, the nonREM-REM cycle ensues. The circadian rhythm also affects the relationship between REM and nonREM 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 cycle [13].

Sleep pathologies and current treatements

Disorder	Clinical features	Underlying deficit	Common treatments
Insomnia	Inability to fall asleep; feelings of inadequate sleep (not shorted sleep)	Unknown in most cases; rarely, brain lesion.	Behavior modification
Sleep apnea	Interrupted, obstructed breathing, causing hypoxia	Small airways and reduced tone in airway muscles during sleep	Continuous Positive Airway Pressure (CPAP) which is delivered through a mask
REM behavior disorder	Acting out of dreams; injury during sleep	Brainstem damage	Clonazepam
Periodic leg movements	Regular twitches, usually of the legs	Unknown; potentially a brainstem abnormality?	Benzodiazepines; dopamine agonists
Narcolepsy	Sleepiness; cataplexy	Loss of hypocretin neurons, increased number of histamine neurons	Stimulants for sleepiness; antidepressants or norardrenergic agonists for cataplexy

Why we sleep

There is little agreement on the functional role of sleep states [6-9]. Daily sleep duration varies tremendously across mammalian species, ranging from 2 to 20 hours. The variation in duration is not strongly correlated with brain size or brain-body weight ratio, but is linked to diet, with herbivores sleeping the least and carnivores sleeping the most[6]. This pattern is consistent with an adaptative role for sleep in aquiring food and conserving energy.

Abbreviations: AH, anterior hypothalamus; DR, dorsal raphe; EEG, electroencephalogram; EMG, electromyogram; GABA, gamma-aminobutyric acid; gr, gracile fasciculus; Hcrt, hypocretin (orexin); His, histamine; IMM, intermedio-medial nucleus; IO, inferior olive; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LSp, lateral spinal nucleus; MCH, melanin concentrating hormone; MIA, medullary inhibitory area; NB, nucleus basalis; NTS, nucleus of the solitary tract; PaR, pararubral nucleus; PGO, ponto-geniculo-occipital; PPT, pedunculopontine tegmental nucleus; PZ, parafacial nucleus; R, red nucleus; SCN, suprachiasmatic nucleus; vlPAG, ventrolateral periaqueductal grey; 7N, seventh nerve nucleus.