

Review article

Neural circuitry underlying REM sleep: A review of the literature and current concepts

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ABSTRACT

As one of the fundamental sleep states, rapid eye movement (REM) sleep is believed to be associated with dreaming and is characterized by low-voltage, fast electroencephalographic activity and loss of muscle tone. However, the mechanisms of REM sleep generation have remained unclear despite decades of research. Several models of REM sleep have been established, including a reciprocal interaction model, limit-cycle model, flip-flop model, and a model involving γ -aminobutyric acid, glutamate, and aminergic/orexin/melanin-concentrating hormone neurons. In the present review, we discuss these models and summarize two typical disorders related to REM sleep, namely REM sleep behavior disorder and narcolepsy. REM sleep behavior disorder is a sleep muscle-tone-related disorder and can be treated with clonazepam and melatonin. Narcolepsy, with core symptoms of excessive daytime sleepiness and cataplexy, is strongly connected with orexin in early adulthood.

1. Introduction

People spend nearly one-third of their lives sleeping. Adequate sleep underlies optimal physical condition. Without enough sleep, people may suffer detrimental effects on brain restitution, synaptic homeostasis, memory consolidation, and task learning. Hence, the unique functions and mechanisms of sleep generation and maintenance have been investigated extensively.

With the development and implementation of electroencephalography (EEG), electromyography, and electrooculography, vigilance states have been divided into the following stages: wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. In general, wakefulness is represented by high-frequency low-voltage waves and high muscle tone. NREM sleep is defined by higher voltage, slower waves, and decreased muscle tone, while REM sleep is characterized by low-voltage fast EEG activity, dreaming, and complete loss of muscle tone (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957).

NREM sleep is typically accompanied by increased slow wave activity, during which synchronous neuronal discharge occurs (Aserinsky and Kleitman, 1953). In contrast, during REM sleep, cholinergic neurons discharge asynchronously; Intravenous injection of an anticholinesterase eserine sulphate in the decerebrate cat activates cholinergic neurons located in the brainstem reticular formation and reproduces postural atonia typical of desynchronized sleep by using long-term recordings of single units neurons (Hoshino and Pompeiano, 1976; Pompeiano, 1975). REM sleep, which has also been referred to as “paradoxical sleep” by Michel Jouvet, is thought to be a cortical state closer to that of wakefulness than to NREM sleep and an independent state of alertness. Evidence has supported that the process of human memory consolidation is strongly dependent on REM sleep; however, selective disruption of REM sleep results in no performance gain, while NREM sleep disruption does not affect improvement on the performance of a basic visual discrimination task (Karni et al., 1994). Complex associative (spatial) learning has been shown to be persistently impaired

Abbreviations: CNZ, clonazepam; DLB, dementia with Lewy bodies; DMH, dorsomedial hypothalamic nucleus; DPGi, dorsal paragigantocellular nucleus; DRN, dorsal raphe nucleus; EDS, excessive daytime sleepiness; EEG, electroencephalogram; GABA, γ -aminobutyric acid; HCRT, hypocretin; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamic area; LPGi, lateral paragigantocellular nucleus; LPT, lateral pontine tegmentum; MCH, melanin-concentrating hormone; NREM, non-REM; PD, Parkinson’s disease; PGO, ponto-geniculo-occipital; PnO, oral pontine reticular nucleus; PPT, pedunculopontine tegmental nucleus; PRF, pontine/mesencephalic reticular formation; RBD, REM sleep behavior disorder; REM, rapid eye movement; SLD, sublateral dorsal tegmental nucleus; SubC, subcoeruleus nucleus; vIPAG, ventrolateral periaqueductal gray matter; vMM, ventromedial medulla.

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by restricting REM sleep for a short critical period each day (Bjorness et al., 2005). However, REM sleep perturbation itself is stressful and resulting in a general cognitive impairment. The hypothalamic-pituitary-adrenal axis takes responsibility for the core hormonal response caused by homeostatic changes. And several procedures were used to reduce stress in these experiments as follows: (a) multiple platforms were used to reduce immobility stress; (b) the water level was adjusted below the platform avoiding the animals' tails touch the water; (c) the animals were allowed to drink fresh water at all times; and (d) the period of restriction lasted only for four hours (Bjorness et al., 2005). Theta activities during REM sleep show a relationship with emotional memory consolidation (Boyce et al., 2016). Interestingly, when researchers investigated REM sleep in the platypus, they found that EEG in this state exhibits a moderate or high voltage, which has been characterized as NREM sleep in adult placental and marsupial mammals (Siegel et al., 1999). Therefore, an increasing number of studies have supported that low-voltage EEG is indicative of mammalian REM sleep (Siegel et al., 1999). In addition, data have suggested that the percentage of REM sleep is much higher in children and younger mammals such as rats, which spend the majority of their early lives in REM sleep (Blumberg et al., 2005; Roffwarg et al., 1966). REM sleep varies considerably across different species (Peever and Fuller, 2017). Importantly, all recent discoveries related to REM sleep would not have been possible without the landmark discovery of REM sleep in 1953.

For many years, most studies investigating sleep regulation have focused on NREM sleep. In contrast, little attention has been devoted to elucidating REM sleep. Hence, the mechanisms underlying the regulation of REM sleep have remained unclear. In this review, we focus on current knowledge regarding mechanisms controlling REM sleep and two typical REM-sleep-related disorders, namely REM sleep behavior disorder (RBD) and narcolepsy.

2. REM sleep-circuitry assessment

2.1. General characteristics of REM sleep

REM sleep (also called paradoxical sleep) is a sleep state paradoxically associated with highly synchronized discharges of theta rhythms (4–8 Hz) activity and muscle atonia. Furthermore, REM sleep only appears in mammals (Siegel et al., 1998), especially at a young age (Roffwarg et al., 1966). The characteristics of REM sleep are as follows: (a) hippocampal theta oscillations, which are signs of REM sleep in rodents and can be divided into two types of activity, namely type I (4–7 Hz) and type II (7–12 Hz) (Shin et al., 2005); (b) ponto-geniculo-occipital (PGO) waves, which are field potentials generated from the cholinergic brain stem, the pons, lateral geniculate nucleus, and occipital cortex since intraperitoneal injection of anticholinergic agent atropine sulfate to cats blocked the occurrence of bursts of PGO waves (Henriksen et al., 1972), while lesions of these regions abolished PGO waves which was induced by intravenous injection of an anticholinesterase eserine sulphate (Magherini et al., 1971), indicate onset of REM sleep (Jacobs et al., 1972); (c) cortical activation, which arises from excitatory inputs of the activated thalamic basal forebrain, including the horizontal limb of the diagonal band, substantia innominata, and magnocellular preoptic region (Lee et al., 2005, 2004; Takahashi et al., 2009); (d) muscle atonia, which results from active inhibition such as from increased levels of γ -amino butyric acid (GABA) and glycine (Chase et al., 1989; Xi et al., 2001) and de-facilitation of excitatory inputs from the brain stem (Fenik et al., 2005); (e) REM in both tonic (postural muscle atonia) and phasic (cranial muscle twitching of the jaw, whisker, and tongue muscles) states, which are regulated by separate brainstem neural circuits (Anaclet et al., 2010; Marquez-Ruiz and Escudero, 2008); and (f) changes in heart and breathing rates, as well as body temperature (Monti et al., 2002; Negoescu and Csiki, 1989).

2.2. Neural foundation underlying REM sleep regulation

REM sleep is generally thought to be generated from interactions between cholinergic laterodorsal/pedunculopontine tegmental nucleus (LDT/PPT) and the glutamatergic pontine/mesencephalic reticular formation (PRF) (Elazar and Berchanski, 2001; Thakkar et al., 1996). Experiments using a variety of techniques—such as ablations, lesions, pharmacology, immunohistochemistry, and electrophysiological recordings (Jones, 1991; Jouvet, 1962; Sakai and Koyama, 1996; Vanni-Mercier et al., 1989)—have indicated that neurons in the brain stem and dorsolateral pons, especially the sublaterodorsal tegmental nucleus (SLD; equivalent to the subcoeruleus nucleus [SubC]) (Sakai et al., 2001), are responsible for controlling REM sleep (Boissard et al., 2002; Jones, 1991; Jouvet, 1962; Vanni-Mercier et al., 1989). Neurons in the medulla, such as GABAergic neurons in the ventral and dorsomedial medulla (Verret et al., 2006; Weber et al., 2015), especially the lateral paragigantocellular nucleus (LPGi), are believed to act as REM-sleep-active neurons (Sapin et al., 2009), participating in REM sleep muscle atonia (Magoun and Rhines, 1946; Schenkel and Siegel, 1989), sleep transitions, and REM sleep maintenance (Liu and Dan, 2019). In addition, inhibition of A_{2A} receptor neurons in the olfactory bulb increases REM sleep (Wang et al., 2017, 2012). However, greater attention has been focused on the role of glutamatergic neurons in REM sleep generation, as the selective elimination of glutamatergic neurotransmission reduces REM sleep (Krenzer et al., 2011). Cell-type-specific microendoscopic calcium imaging demonstrates that glutamatergic neurons are maximally active during REM sleep (Cox et al., 2016), and juxtacellular recording and labeling in naturally sleeping-waking also show that some glutamatergic neurons are REM sleep maximally active (Boucetta et al., 2014). Taken together, REM sleep regulation is modulated by several neural circuits, including noradrenergic, serotonergic, cholinergic, glycinergic, GABAergic, and glutamatergic neurons (Boissard et al., 2003; Brown et al., 2008; Clement et al., 2011; Ford et al., 1995; Lu et al., 2006; Maloney et al., 1999, 2000). Furthermore, these findings have promoted the development of several animal models for elucidating the mechanisms underlying REM sleep regulation, which we discuss below.

2.3. Summary of models reported in studies of REM sleep circuits

2.3.1. Reciprocal interaction model

McCarley and Hobson proposed a reciprocal interaction model to explain conversion between REM-on and REM-off states (Hobson et al., 1975; McCarley and Hobson, 1975). REM-on refers to a group of neurons whose firing rates increase when REM sleep is initiated and maintained, while REM-off refers to neurons with an opposite pattern of activity. In this model, cholinergic neurons in the LDT and PPT are REM-on neurons (Hobson et al., 1975; McGinty and Harper, 1976), whereas noradrenergic and serotonergic neurons are proposed to be REM-off neurons (el Mansari et al., 1989; Kayama et al., 1992; Steriade et al., 1990).

The activity pattern of this model hypothesizes that REM-on neurons are inhibited by activated REM-off neurons during wakefulness and NREM sleep. When the firing of REM-off neurons decreases, REM-on neurons are disinhibited and local REM sleep is initiated. As a result, downstream effectors of REM-on neurons are stimulated, generating REM sleep. In addition, activity of REM-on neurons is enhanced via mutual positive feedback to stabilize the REM sleep state. Furthermore, REM-on neurons send excitatory projections to REM-off neurons to gradually arouse the REM-off state. In this model, the activity of presumed REM sleep related neurons (i.e., cholinergic and aminergic neurons) keeps pace with alternations between sleep states (Hobson et al., 1975; Lydic et al., 1983; Thakkar et al., 1998); The LDT and PPT send cholinergic projections to reticular formation areas (e.g., the oral pontine reticular nucleus [PnO] and caudal pontine reticular nucleus regions) (Mitani et al., 1988) and activate aminergic neurons (Li et al., 1998). The cholinergic agonist, carbachol, activates reticular neurons

through ionotropic nicotinic and muscarinic receptors (Greene et al., 1989; Stevens et al., 1993). Cholinergic neurons in the LDT/PPT receive signals from serotonergic neurons in the dorsal raphe nucleus (DRN) and median raphe nuclei as well as noradrenergic neurons in the locus coeruleus (LC) (Pickel et al., 1974; Semba and Fibiger, 1992). Norepinephrine and 8-hydroxy-2-dipropylaminotetralin (5-HT_{1A} agonist) can inhibit brain stem cholinergic neurons (Thakkar et al., 1998; Williams and Reiner, 1993). Enhancement of cholinergic tone or attenuation of aminergic tone promotes REM sleep (i.e., decreases REM sleep latency and increases the amount of REM sleep (Kubin, 2001; Lauriello et al., 1993; Reid et al., 1994)) or inhibits REM sleep (Rauniar et al., 1998) reversely. In human and animal models, most monoaminergic and noradrenergic antidepressants can effectively suppress REM sleep.

This model has several limitations. Many studies have presented evidence that is inconsistent with this model. For example, LDT/PPT/LC lesions do not significantly change the amount of REM sleep (Blanco-Centurion et al., 2004), and the duration of REM sleep is significantly decreased in muscarinic (M)3^{-/-} but not in M2/M4^{-/-} mice (Goutagny et al., 2005). In addition, the number of activated cholinergic neurons is not increased during the REM sleep rebound period after selective REM sleep deprivation (Verret et al., 2005). In addition, this model neglects the influence of circadian rhythms and excludes the role of descending pathways from the forebrain.

2.3.2. Limit-cycle model

The limit-cycle model is a reciprocal interaction model and has been proposed by McCarley and colleagues (Brown et al., 2012; Massaquoi and McCarley, 1992; McCarley and Massaquoi, 1986). The brain stem contains a large number of GABAergic neurons. Anatomical studies have confirmed that these neurons interact with REM-sleep-related regions (Boissard et al., 2003; Brown et al., 2008; Ford et al., 1995; Maloney et al., 2000; Sapin et al., 2009). Furthermore, this model takes into consideration the circadian influence of the REM oscillator and the role of local GABAergic neurons.

The general framework of this model is as follows. LDT/PPT cholinergic neurons, which act as REM-on neurons, exhibit excitatory interactions with glutamatergic neurons in the PRF to promote REM sleep. They also excite GABAergic interneurons that send inhibitory projections to DRN serotonergic and LC noradrenergic REM-off neurons as well as to neurons responsible for inhibiting PRF glutamatergic neurons in the REM sleep state. As REM sleep progresses, REM-on neurons gradually activate REM-off neurons to reverse the sleep state. In contrast, REM-off neurons inhibit REM-on neurons during wakefulness and NREM sleep. There is also mutual negative feedback among REM-off neurons to facilitate the onset of REM sleep (Dunmyre et al., 2014).

Based on the previous reciprocal interaction model, additional evidence has been presented. Retrograde tracing experiments have indicated that GABAergic neurons in the PnO, lateral pontine tegmentum (LPT), and ventrolateral periaqueductal gray matter (vPAG) project to the SubC in rats (Boissard et al., 2003; Lu et al., 2006). In cats and rats, bicuculline (GABA_A receptor antagonist) acting on the SubC or PnO has an inhibitory effect on the REM sleep state (Sanford et al., 2003; Xi et al., 1999), whereas muscimol (GABA_A receptor agonist) enhances REM sleep by inhibiting the vPAG and LPT (Sapin et al., 2009; Schenck et al., 1993). However, a line of evidence suggests that REM sleep is not affected by inactivating GABAergic and glycinergic neurotransmission in the caudal LDT-SLD and vPAG-LPT regions (Krenzer et al., 2011). GABAergic neurons surrounding the LC are activated when rats recover from REM sleep deprivation (Maloney et al., 1999), and the cholinergic agonist, carbachol, excites SubC GABAergic neurons (Brown et al., 2008). Retrograde tracing experiments have confirmed that the DRN receives GABAergic inputs from the rostral PnO and vPAG/LPT, and the LC receives GABAergic input from REM-on neurons (Sapin et al., 2009; Verret et al., 2006). Microdialysis has shown that GABA levels are increased in the LC and DRN during REM sleep compared with those

during the waking state (Nitz and Siegel, 1997a, b).

2.3.3. Flip-flop model

Ablation of cholinergic and monoaminergic nuclei in the brain stem has only a limited influence on REM sleep (Jones et al., 1977; Lu et al., 2006; Mouret and Coindet, 1980), which contradicts earlier models. Therefore, it is doubtful that interactions between these two cell groups are necessary for REM sleep (Lu et al., 2006). This model suggests that REM sleep arises from reciprocal inhibition between REM-off (i.e., vPAG and LPT) and REM-on (i.e., SLD, precoeruleus, and LDT/PPT) regions.

This flip-flop switch shows that REM-off neurons are dominated by the extended ventrolateral preoptic nucleus, LC, DRN, LDT/PPT, and SLD. Meanwhile, GABAergic neurons in the vPAG and LPT also inhibit REM-on neurons in the SLD and precoeruleus (Hayashi et al., 2015; Weber et al., 2015). Furthermore, it is noteworthy that glutamatergic neurons in the vPAG and LPT also negatively regulate REM sleep (Kashiwagi et al., 2020; Zhong et al., 2019). In support of this model, microinjection of bicuculline or kainic acid into the SLD leads to the enhancement of REM sleep (Onoe and Sakai, 1995). Tract-tracing studies have found that GABAergic and glutamatergic neurons in the SLD project to the vPAG and LPT, while the projections from the vPAG and LPT to the SLD are GABAergic (Boissard et al., 2003; Hayashi et al., 2015; Kashiwagi et al., 2020; Lu et al., 2006). In addition, LPT GABAergic neurons also project to the lateral hypothalamic area (LH) and the DRN, which regulates REM sleep and muscle tone (Chen et al., 2019). Furthermore, orexinergic neurons are suppressed during REM sleep (Takahashi et al., 2008), and a deficiency in this process may be a cause of narcolepsy (Thannickal et al., 2000). Collectively, the major function of this switch is to stabilize the REM-on or REM-off state (Hanriot et al., 2007).

2.3.4. A model involving GABAergic, glutamatergic, and aminergic/orexin/melanin-concentrating hormone (MCH) neurons

Many studies have demonstrated that cholinergic and aminergic neurons act as modulators in REM sleep control. Coexpression of Fos and vesicular glutamate transporter 2 in the SLD during recovery from REM sleep deprivation suggests that glutamatergic neurons have a considerable impact on the REM-on state (Lu et al., 2006; Valencia Garcia et al., 2017). Studies have shown that the SLD sends direct projections to GABAergic and glycinergic neurons in the spinal cord (Clement et al., 2011), as well as to the nucleus raphe magnus, ventral gigantocellular reticular nucleus, alpha gigantocellular reticular nucleus, and LPGi (Boissard et al., 2002) to control atonia (Verret et al., 2006). This glutamatergic signaling also affects the posterior hypothalamus, basal forebrain, and intralaminar thalamic nuclei (Luppi et al., 2013), which may cooperate with activated LDT/PPT cholinergic neurons and reticular formation glutamatergic neurons to result in cortical activation (Boissard et al., 2002; Valencia Garcia et al., 2017).

This model emphasizes the importance of the LH especially MCH neurons in REM sleep onset and maintenance. MCH neurons occupy approximately one-third of activated GABAergic LH neurons during the REM recovery period (Hanriot et al., 2007; Sapin et al., 2010). Activated MCH neurons send inhibitory inputs to vPAG GABAergic neurons, monoaminergic REM-off neurons, histaminergic neurons, and hypocretinergic neurons, which contribute to the generation of REM sleep (Arrigoni et al., 2019; Luppi et al., 2013). REM-sleep-active MCH neurons in the hypothalamus are also involved in active forgetting in the hippocampus (Izawa et al., 2019).

The role of SLD neurons in the regulation of REM sleep is complicated. Valencia et al. found that SLD neurons are involved in muscle atonia rather than REM sleep generation; SLD neurons do not innervate the intralaminar thalamus but only send descending projections to GABAergic/glycinergic neurons in the ventral medulla, which plays a crucial role in muscle atonia (Valencia Garcia et al., 2017). Chemo-genetic activation of SLD glutamatergic neurons results in an immediate

increase in wakefulness and subsequent increase in REM sleep (Erickson et al., 2019). However, glutamatergic neurons in the SLD that are positive for *Atoh1* also negatively regulate REM sleep (Hayashi et al., 2015).

A similar finding was made by Horner et al. (Grace and Horner, 2015; Valencia Garcia et al., 2017). They found that activation of PPT cholinergic inputs to the SubC enhances REM sleep, while SubC cholinergic receptor antagonism does not yield an opposite effect. Furthermore, local blockage of cholinergic receptors in the SubC does not disrupt the onset of REM sleep. These findings support a minor role of pontine cholinergic input in modulating the transition from NREM to REM sleep, but not in generation of REM sleep. This research group has further proposed that the roles of nuclei in REM sleep control cannot be determined by gain-of-function experiments; instead, loss-of-function experiments are required (Grace and Horner, 2015; Grace et al., 2014).

3. Diseases involved in dysfunction of REM sleep circuits

Sleep disruption is strongly linked with impairment of human cognitive, emotional, and executive performance. The studies on the mechanism of REM sleep will provide a basis for the treatment of REM sleep related diseases. In this section, we review two typical REM sleep disorders, RBD and narcolepsy.

3.1. REM sleep parasomnia

Parasomnia is used to describe a series of dissociated sleep disorders characterized by undesirable and unpleasant behaviors or experiential phenomena that always occur around or during sleep, such as somnambulism (sleepwalking) and sleep terrors (nightmares) (Ylikoski et al., 2014). Parasomnias may occur during NREM sleep, sleep-wake transitions, and REM sleep. According to the International Classification of Sleep Disorders (Medicine, 2014), three main disorders are recognized as REM sleep parasomnias: nightmare disorder, recurrent isolated sleep paralysis, and RBD.

Nightmares are defined as disturbing mental experiences that seem vivid and might lead to a wide range of negative emotions (e.g., fear, anxiety, and anger) and somatic manifestations (e.g., tachycardia, sweating, and tachypnea). Recurrent isolated sleep paralysis is recognized as a persistence of REM sleep into wakefulness when the sleeper awakes with muscle atonia. RBD is characterized by an absence of muscle atonia during REM sleep (REM sleep paralysis), thereby inducing an acting out dreams (Medicine, 2014). These sleep behaviors usually enact fight-or-flight reactions and appear in violent dreams (Tinuper et al., 2007).

Compared with the other two REM sleep parasomnias, RBD has attracted much more attention. It has been shown that RBD is highly associated with synucleinopathy-related neurodegenerative disorders, especially Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy, and pure autonomic failure (Boeve et al., 2001). RBD can precede the onset of neurodegenerative clinical manifestation by years to decades (Boeve, 2010; Boeve et al., 2013, 2003b). A 16-year update study reported that 80.8 % of patients initially diagnosed with RBD developed a parkinsonism/dementia (Schenck et al., 2013). It has been shown that more than one-third of patients with PD share a secondary or symptomatic RBD, and most of them experience other parasomnias and/or isolated sleep symptoms (Ylikoski et al., 2014).

3.2. Narcolepsy

Narcolepsy is a rare neurological disorder that involves the central nervous system. It affects approximately 0.026–0.050 % of the population (Ohayon et al., 2002), and the first symptoms often (>50 %) develop during adolescence or young adulthood (Dauvilliers et al., 2001). Narcolepsy has core symptoms of excessive daytime sleepiness (EDS) and cataplexy, and presents with disordered regulation of REM sleep with sudden episodes of partial or complete paralysis of voluntary

muscles (sleep paralysis), as well as emotional (depression), sleep-wake (disturbed sleep), and metabolic (obesity) disturbances (Scammell, 2015). To aid diagnosis, symptoms are organized into the classic tetrad as follows (Yoss and Daly, 1957): (1) EDS: sudden or persistent falling asleep during the day, irrespective of the amount or quality of sleep the night before; (2) cataplexy: sudden loss of muscle tone, which is usually triggered by positive emotion rather than negative emotional stimuli and may lead to disinhibition of REM sleep atonia circuitry by activating neurons in the amygdala and median prefrontal cortex (Anic-Labat et al., 1999); (3) hypnagogic hallucinations: starting sleep with unreal, vivid auditory or visual perceptions; and (4) sleep paralysis/temporary inability: temporarily unable to move while awakening or falling asleep. According to the International Classification of Sleep Disorders (Medicine, 2014), narcolepsy can be differentiated into two types. Type 1 refers to narcolepsy with cataplexy, and type 2 refers to narcolepsy without cataplexy (Sateia, 2014).

Hypocretin (HCRT/orexin), a neuropeptide produced by neurons in the posterior hypothalamus, is believed to be associated with the pathogenesis of narcolepsy. It has been reported that complex immune-mediated processes induced by genetic and environmental factors are the primary cause of loss of HCRT neurons and their projections to wake-promoting regions, which may result in the onset of narcolepsy with cataplexy (Liblau et al., 2015; Nishino et al., 2000). Similar to paralysis of REM sleep (Burgess and Scammell, 2012), cataplexy associated with narcolepsy is thought to be driven by an imbalance between cholinergic and monoaminergic systems in the pons resulting from monoaminergic hypoactivity and cholinergic hypersensitivity (Boehme et al., 1984; Mefford et al., 1983).

4. Discussion

4.1. Networks underlying REM sleep

To explain all the transitions among wake, REM sleep, and NREM sleep states, Dan et al. proposed an arousal-action model (Liu and Dan, 2019), which includes wakefulness-, REM sleep-, and NREM sleep-promoting neurons. Additionally, the REM-sleep-promoting neurons in the arousal-action model include several neuronal types, such as the following: cholinergic, GABAergic, galanin-expressing, and glutamatergic neurons and related brain regions; the dorsomedial hypothalamic nucleus (DMH), DPGi, LDT, LPGi, preoptic area, PPT, raphe pallidus area, and SLD (Liu and Dan, 2019). Based on the above information, here we summarize networks underlying REM sleep regulation. For REM sleep generation and maintenance, neurons in the preoptic area, LH, and DMH are activated. In addition, DMH galanin-expressing neurons send inhibitory signals to the raphe pallidus area and SLD neurons project to the vlPAG and LPT to release their suppression on REM-on neurons. Furthermore, SLD neurons also project to GABAergic and glycinergic neurons in the spinal cord, and neurons in the LPGi/DPGi (the majority of which are GABAergic neurons) also project to the spinal cord. The networks underlying REM sleep are summarized in Fig. 1.

4.2. Degeneration of REM sleep networks in RBD

The pathogenesis of RBD is believed to be associated with a degenerative breakdown of the brain stem network that controls REM sleep (Peever et al., 2014). Lesions of the pontine tegmentum and ventromedial medulla in cats, rats, and mice produce RBD-like behaviors (Hendricks et al., 1982; Holmes and Jones, 1994). Neuroimaging studies in RBD patients have revealed structural damage in the midbrain tegmentum and rostral pons (Scherfler et al., 2011). Post-mortem studies of patients with RBD and subsequent PD or DLB have also revealed neuronal cell loss and Lewy pathology in the brainstem nuclei that regulate REM sleep paralysis, such as the LC, PPT, gigantocellular reticular nucleus, and amygdala (Iranzo et al., 2013).

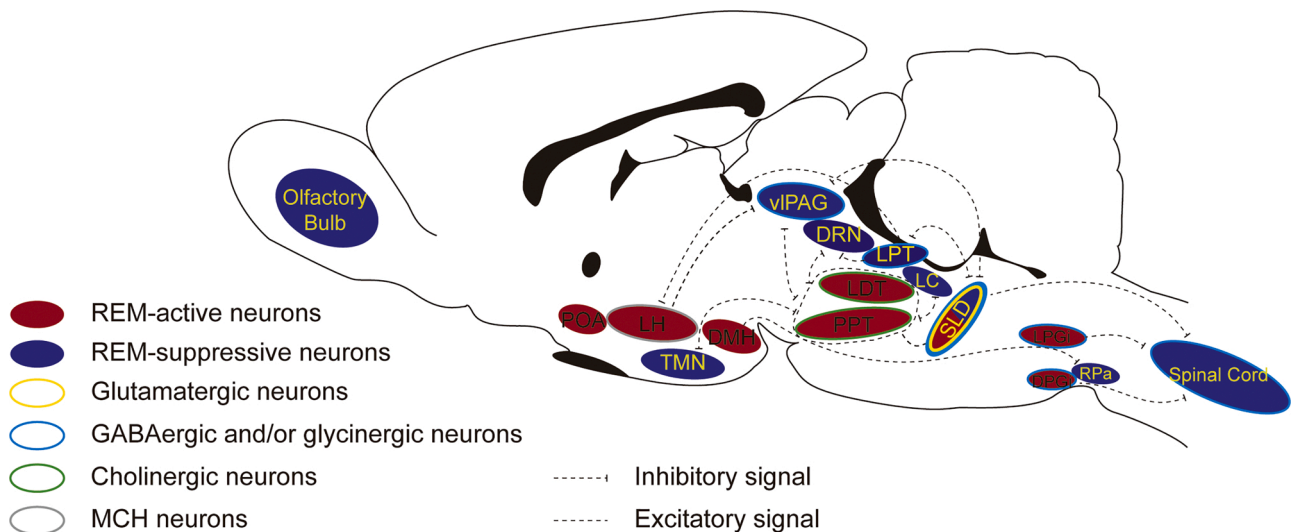


Fig. 1. Summary of REM sleep networks. SLD glutamatergic neurons are critical in the regulation of REM sleep. For REM sleep maintenance and muscle atonia, cholinergic neurons in the LDT/PPT are important, as are GABAergic neurons in the LPGi, DPGi, VIPAG, LPT, and spinal cord. The dashed lines in the figure show the connectivities between the different groups of neurons. REM-active neurons are excited and directly or indirectly inhibit REM-suppressive neurons to generate and maintain REM sleep.

During physiological REM sleep, paralysis is elicited by inhibiting somatic motor neurons that receive hyperpolarizing signals from GABAergic/glycinergic neurons in the ventromedial medulla (vMM) (Arrigoni et al., 2016; Brooks and Peever, 2012; Schenkel and Siegel, 1989). Luppi et al. has proposed a neurotransmission imbalance hypothesis of RBD in which REM-on glutamatergic neurons in the SLD induce muscle atonia (Torontali et al., 2019) by projecting to premotor GABAergic/glycinergic neurons in the vMM, such as the ventral gigantocellular reticular nuclei and nucleus raphe magnus. However, the neurodegenerative damage in RBD disturbs this glutamatergic and GABAergic/glycinergic network (Luppi et al., 2011). Transgenic mice with deficient glycine and GABA_A receptor function exhibit RBD-like behaviors that can be rescued by treatment with clonazepam (CNZ). Melatonin is also involved in impaired inhibitory neurotransmission in RBD pathogenesis (Brooks and Peever, 2011). However, there are more complex modulatory mechanisms beyond a direct glutamate-GABA/glycine pathway in the SLD and vMM. According to the REM sleep flip-flop switch theory proposed by Lu et al., both REM-on and REM-off regions in the mesopontine tegmentum contain GABAergic neurons and inhibit each other (Lu et al., 2006). This research group also found a restricted region in the ventromedial medulla, termed the supraolivary medulla, which sends glutamatergic projections to the spinal ventral horn. A study of mice that were modified using loxP showed that lesioning of the supraolivary medulla glutamate but not GABA/glycine release resulted in a loss of muscle atonia (Vetrivelan et al., 2009). Another investigation showed that antagonistic blockade of phasic GABAergic/glycinergic drive at the trigeminal motor pool does not prevent or reverse REM atonia. These results might implicate another inhibitory mechanism mediating REM atonia (Brooks and Peever, 2008). Furthermore, neurochemical lesioning of the caudal ventral mesopontine junction causes an increase in phasic motor activity during REM sleep, which suggests that this network is more complicated than previously estimated (Lai et al., 2008).

4.3. Treatment of RBD

Similar to the other two parasomnias, in which cognitive behavioral therapies and reassurance are regarded as the first-line treatment (Galbiati et al., 2015), maintaining a safe sleep environment is helpful in treating RBD (Aurora et al., 2010). Any situations that trigger or exacerbate RBD should be avoided in non-pharmacological interventions,

including sleep deprivation, insomnia, sleep-disordered breathing, and the use of improper drugs (Bassetti and Bargiotas, 2018). CNZ and melatonin have been regarded as the most effective RBD pharmacological interventions (Bassetti and Bargiotas, 2018). CNZ, a long-lasting benzodiazepine, is indicated as the first-line therapy (Aurora et al., 2010) and has been proven to be efficient in controlling violent dreams and sleep disturbances of RBD patients (Schenck et al., 1993). However, side effects, such as daytime somnolence, confusion, falls, and exacerbation of sleep apnea, should be monitored (Anderson and Shneerson, 2009). Another effective medication is melatonin, which is suggested for patients for whom CNZ is contraindicated, such as those with dementia, gait disorders, or obstructive sleep apnea syndrome (Aurora et al., 2010). Melatonin is safer and more tolerable than clonazepam and has a more limited potential for drug-drug interactions (McGrane et al., 2015). In addition, melatonin is helpful for RBD patients with other neurological disorders such as PD, DLB, multiple system atrophy, narcolepsy, and Alzheimer's disease (Boeve et al., 2003a). After a six-week treatment with melatonin, polysomnographic recordings showed a significant reduction in REM sleep without muscle atonia, as well as a reduction in the number of REM sleep stage-shifts and epochs (Kunz and Bes, 1999). A melatoninergic agonist, ramelteon, has also exhibited potential for the treatment of RBD and its related disorders (Kashihara et al., 2016). The dopamine receptor agonist, pramipexole, is contradictory in RBD treatment (Kumru et al., 2008; Schmidt et al., 2006). The antidepressant, paroxetine, as well as L-3,4-dihydroxyphenylalanine and the acetylcholinesterase inhibitor, donepezil, have also been studied as alternative treatments for RBD; however, the results have been limited. While new insights have been elucidated for dopaminergic agonists, glutamatergic antagonists, and phytocannabinoids, further evidence is needed to support their effectiveness and safety (de Almeida et al., 2018). The effectiveness of other interventions, such as behavioral measures (Alariste-Booth et al., 2015) or deep brain stimulation (Eugster et al., 2016), is still deemed inconclusive.

4.4. Treatment of narcolepsy

In 1960, it was first documented that the tricyclic antidepressant, imipramine, could significantly decrease the occurrence of cataplexy via its active metabolite, desipramine; however, there was no obvious effects on EDS and irresistible sleep attacks (Akimoto et al., 1960). Tricyclic antidepressants—such as imipramine, protriptyline, and

clomipramine—have been shown to control sleep paralysis and hypnagogic hallucinations, as well as to inhibit REM sleep. However, their utility is limited by frequent and intolerable side effects, such as sedation, sweating, constipation, and tachycardia, caused by non-selective blockage of serotonergic and noradrenergic reuptake (Mignot, 2012). Similarly, selegiline, a monoamine oxidase inhibitor with sympathomimetic side effects, shows a strong suppression of REM sleep and great improvement in EDS (Hublin et al., 1994).

Current treatments for narcolepsy are symptomatic and based on management of sleepiness and cataplexy. They include wake-promoting therapeutics that enhance presynaptic dopaminergic release and anti-cataplectic agents that facilitate monoaminergic neurotransmission. First-line medications for EDS are stimulants and include modafinil/armodafinil, pitolisant, and sodium oxybate (Black et al., 2016; Darwish et al., 2009; Dauvilliers et al., 2013; Group, 2005). For cataplexy, sodium oxybate, venlafaxine, and pitolisant are regarded as first-choice treatments (Alshaikh et al., 2012; Thorpy, 2015). Sodium oxybate, the sodium salt of gamma-hydroxybutyrate, increases slow wave activity of NREM sleep after administration (Black et al., 2010; Walsh et al., 2010). Its therapeutic mechanism might be indirect, involving dopaminergic transmission and secondary interactions with GABA_B receptors (Huang and Guilleminault, 2009) possibly through disinhibition of dopaminergic release via G-protein-coupled inwardly rectifying potassium channels (Cruz et al., 2004). Another effective medication is modafinil, which inhibits dopamine reuptake via the dopamine transporter (Wisor, 2013). Modafinil might exert its effects by acting on components of wake-promoting systems that are facilitated as a compensatory response to disrupted HCRT signaling (Willie et al., 2005). Methylphenidate and amphetamines are now second- and third-line therapies, respectively. They are used to counter EDS in narcolepsy as a supplement to modafinil or sodium oxybate (Thorpy and Dauvilliers, 2015). In addition, the increase of histaminergic tone caused by histamine H₃ autoreceptor antagonism is thought to exert therapeutic effects on EDS in narcolepsy (Black et al., 2017). Pitolisant has received approval as a new drug for the treatment of narcolepsy in Europe via boosting hypothalamic levels of histamine (Calik, 2017; Irukayama-Tomobe and Yanagisawa, 2018). However, adverse reactions still exist, such as headache, anxiety, irritability, and nausea (Yang and Gao, 2019). R-baclofen, a GABA_B agonist with an enantiomer-specific form of racemic baclofen, has been considered a narcolepsy therapeutic in a preclinical study (Black et al., 2014).

Recently, Yang et al. reported that a selective dopamine and norepinephrine reuptake inhibitor, solriamfetol, could strongly reduce EDS in patients with narcolepsy (Yang and Gao, 2019). Furthermore, it has been approved to be used as a wake-promoting therapy in the USA (Abad and Guilleminault, 2018). The recommended dose is higher than 75 mg but no more than 150 mg once daily (Yang and Gao, 2019).

An underlying auto-immunological mechanism has been proposed for narcolepsy with cataplexy and/or hypocretin deficiency that is characterized by the specific loss of a small number of hypothalamic neurons. T-cell function is responsible for related cell death. Immunotherapy might be a worthwhile strategy for this type of narcolepsy by suppressing T-cell function (i.e., a specific monoclonal antibody reacts with human leucocyte antigen attached HCRT fragments). Although immunotherapy is promising, robust evidence is needed before such treatments can be used clinically (Reading, 2019).

When individual management strategies are evaluated, coexisting morbidities, such as depression and additional symptoms (e.g., obesity), should not be neglected (Kallweit and Bassetti, 2017). HCRT replacement compounds and immune-modifying medications are likely to be future treatments (Arias-Carrion and Murillo-Rodriguez, 2014; Baier et al., 2011; Nagahara et al., 2015). If an autoimmune attack on HCRT neurons is the primary cause of narcolepsy, prevention of its development through immunotherapies or neuroprotective strategies may present the most fundamental treatment; however, it is difficult to find enough cases of narcolepsy close to disease onset for well-controlled

studies (Black et al., 2017). Moreover, genetic and stem cell therapies, such as viral vector-based delivery of the prepro-HCRT gene, are also promising choices (Liu et al., 2011).

5. Conclusions

In this review, we summarized the latest progress on the neurobiological mechanisms of REM sleep and REM sleep related diseases. Although there has been much excitement with recent progress in this field, further developments and clinical applications are needed to elucidate more details of the corresponding mechanisms and their effects in patients. In the future, the following studies are needed for better understanding the mechanisms of REM sleep and related diseases: (1) loss-of-function experiments are needed to assess the roles of specific nuclei in REM sleep regulation, such as the LDT, PPT, and/or SLD; (2) additional studies are required to investigate the inhibitory mechanism mediating REM atonia; and (3) evidence supporting the effectiveness and safety of dopaminergic agonists, glutamatergic antagonists, phyto-cannabinoids, and/or deep brain stimulation in RBD treatment is needed.

Furthermore, the onset and maintenance of REM sleep and the transition from NREM to REM sleep still represent critical gaps in our knowledge. In particular, brain regions in the hypothalamus and brainstem (including the pons and medulla oblongata) are likely important regions for further investigation. Therefore, future studies should employ tract-tracing and other specific manipulations of targeted neurons, combined with EEG and other animal behavioral experiments, to determine whether and how NREM-sleep-related nuclei participate in the generation and transition to REM sleep. Furthermore, the most substantial bottleneck is in successfully translating basic research results into the clinical treatment of REM-related diseases. For example, since existing treatments for narcolepsy are all based on mere symptoms, future studies are needed to elucidate the mechanisms of such diseases in order to identify and develop more precise and efficacious treatment strategies.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version, at doi: <https://doi.org/10.1016/j.pneurobio.2021.102106>.

References

- Abad, V.C., Guilleminault, C., 2018. Solriamfetol for the treatment of daytime sleepiness in obstructive sleep apnea. *Expert Rev. Respir. Med.* 1–13.
- Akimoto, H., Honda, Y., Takahashi, Y., 1960. Pharmacotherapy in narcolepsy. *Dis. Nerv. Syst.* 21, 704–706.

- Alatrister-Booth, V., Rodriguez-Violante, M., Camacho-Ordóñez, A., Cervantes-Arriaga, A., 2015. Prevalence and correlates of sleep disorders in Parkinson's disease: a polysomnographic study. *Arq. Neuropsiquiatr.* 73, 241–245.
- Alshaiikh, M.K., Tricco, A.C., Tashkandi, M., Mamdani, M., Straus, S.E., BaHammam, A. S., 2012. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J. Clin. Sleep Med.* 8, 451–458.
- Anacleit, C., Pedersen, N.P., Fuller, P.M., Lu, J., 2010. Brainstem circuitry regulating phasic activation of trigeminal motoneurons during REM sleep. *PLoS One* 5 e8788.
- Anderson, K.N., Shneron, J.M., 2009. Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. *J. Clin. Sleep Med.* 5, 235–239.
- Anic-Labat, S., Guilleminault, C., Kraemer, H.C., Meehan, J., Arrigoni, J., Mignot, E., 1999. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. *Sleep* 22, 77–87.
- Arias-Carrion, O., Murillo-Rodríguez, E., 2014. Effects of hypocretin/orexin cell transplantation on narcoleptic-like sleep behavior in rats. *PLoS One* 9 e95342.
- Arrigoni, E., Chen, M.C., Fuller, P.M., 2016. The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. *J. Physiol.* 594, 5391–5414.
- Arrigoni, E., Chee, M.J.S., Fuller, P.M., 2019. To eat or to sleep: that is a lateral hypothalamic question. *Neuropharmacology* 154, 34–49.
- Aserinsky, E., Kleitman, N., 1953. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 118, 273–274.
- Aurora, R.N., Zak, R.S., Maganti, R.K., Auerbach, S.H., Casey, K.R., Chowdhuri, S., Karipoti, A., Ramar, K., Kristo, D.A., Morgenthaler, T.I., 2010. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J. Clin. Sleep Med.* 6, 85–95.
- Baier, P.C., Hallschmid, M., Seeck-Hirschner, M., Weinhold, S.L., Burkert, S., Diessner, N., Goder, R., Aldenhoff, J.B., Hinze-Selch, D., 2011. Effects of intranasal hypocretin-1 (orexin A) on sleep in narcolepsy with cataplexy. *Sleep Med.* 12, 941–946.
- Bassetti, C.L., Bargiotas, P., 2018. REM sleep behavior disorder. *Front. Neurol. Neurosci.* 41, 104–116.
- Bjorness, T.E., Riley, B.T., Tysor, M.K., Poe, G.R., 2005. REM restriction persistently alters strategy used to solve a spatial task. *Learn. Mem.* 12, 352–359.
- Black, J., Pardi, D., Hornfeldt, C.S., Inhaber, N., 2010. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J. Clin. Sleep Med.* 6, 596–602.
- Black, S.W., Morairty, S.R., Chen, T.M., Leung, A.K., Wisor, J.P., Yamanaka, A., Kilduff, T.S., 2014. GABAB agonism promotes sleep and reduces cataplexy in murine narcolepsy. *J. Neurosci.* 34, 6485–6494.
- Black, J., Swick, T., Bogan, R., Lai, C., Carter, L.P., 2016. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy. *Sleep Med.* 24, 57–62.
- Black, S.W., Yamanaka, A., Kilduff, T.S., 2017. Challenges in the development of therapeutics for narcolepsy. *Prog. Neurobiol.* 152, 89–113.
- Blanco-Centurion, C., Gerashchenko, D., Salin-Pascual, R.J., Shiromani, P.J., 2004. Effects of hypocretin2-saporin and antidiopamine-beta-hydroxylase-saporin neurotoxic lesions of the dorsolateral pons on sleep and muscle tone. *Eur. J. Neurosci.* 19, 2741–2752.
- Blumberg, M.S., Seelke, A.M., Lowen, S.B., Karlsson, K.A., 2005. Dynamics of sleep-wake cyclicity in developing rats. *Proc. Natl. Acad. Sci. U. S. A.* 102, 14860–14864.
- Boehme, R.E., Baker, T.L., Mefford, I.N., Barchas, J.D., Dement, W.C., Ciaranello, R.D., 1984. Narcolepsy: cholinergic receptor changes in an animal model. *Life Sci.* 34, 1825–1828.
- Boeve, B.F., 2010. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann. N. Y. Acad. Sci.* 1184, 15–54.
- Boeve, B.F., Silber, M.H., Ferman, T.J., Lucas, J.A., Parisi, J.E., 2001. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov. Disord.* 16, 622–630.
- Boeve, B.F., Silber, M.H., Ferman, T.J., 2003a. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med.* 4, 281–284.
- Boeve, B.F., Silber, M.H., Parisi, J.E., Dickson, D.W., Ferman, T.J., Benarroch, E.E., Schmeichel, A.M., Smith, G.E., Petersen, R.C., Ahlskog, J.E., Matsumoto, J.Y., Knopman, D.S., Schenck, C.H., Mahowald, M.W., 2003b. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. *Neurology* 61, 40–45.
- Boeve, B.F., Silber, M.H., Ferman, T.J., Lin, S.C., Benarroch, E.E., Schmeichel, A.M., Ahlskog, J.E., Caselli, R.J., Jacobson, S., Sabbagh, M., Adler, C., Woodruff, B., Beach, T.G., Iranzo, A., Gelpi, E., Santamaria, J., Tolosa, E., Singer, C., Mash, D.C., Luca, C., Arnulf, I., Duyckaerts, C., Schenck, C.H., Mahowald, M.W., Dauvilliers, Y., Graff-Radford, N.R., Wszolek, Z.K., Parisi, J.E., Dugger, B., Murray, M.E., Dickson, D. W., 2013. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med.* 14, 754–762.
- Boissard, R., Gervasoni, D., Schmidt, M.H., Barbagli, B., Fort, P., Luppi, P.H., 2002. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur. J. Neurosci.* 16, 1959–1973.
- Boissard, R., Fort, P., Gervasoni, D., Barbagli, B., Luppi, P.H., 2003. Localization of the GABAergic and non-GABAergic neurons projecting to the sublaterodorsal nucleus and potentially gating paradoxical sleep onset. *Eur. J. Neurosci.* 18, 1627–1639.
- Boucetta, S., Cisse, Y., Mainville, L., Morales, M., Jones, B.E., 2014. Discharge profiles across the sleep-waking cycle of identified cholinergic, GABAergic, and glutamatergic neurons in the pontomesencephalic tegmentum of the rat. *J. Neurosci.* 34, 4708–4727.
- Boyce, R., Glasgow, S.D., Williams, S., Adamantidis, A., 2016. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* 352, 812–816.
- Brooks, P.L., Peever, J.H., 2008. Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *J. Neurosci.* 28, 3535–3545.
- Brooks, P.L., Peever, J.H., 2011. Impaired GABA and glycine transmission triggers cardinal features of rapid eye movement sleep behavior disorder in mice. *J. Neurosci.* 31, 7111–7121.
- Brooks, P.L., Peever, J.H., 2012. Identification of the transmitter and receptor mechanisms responsible for REM sleep paralysis. *J. Neurosci.* 32, 9785–9795.
- Brown, R.E., McKenna, J.T., Winston, S., Basheer, R., Yanagawa, Y., Thakkar, M.M., McCarley, R.W., 2008. Characterization of GABAergic neurons in rapid-eye-movement sleep controlling regions of the brainstem reticular formation in GAD67-green fluorescent protein knock-in mice. *Eur. J. Neurosci.* 27, 352–363.
- Brown, R.E., Basheer, R., McKenna, J.T., Strecker, R.E., McCarley, R.W., 2012. Control of sleep and wakefulness. *Physiol. Rev.* 92, 1087–1187.
- Burgess, C.R., Scammell, T.E., 2012. Narcolepsy: neural mechanisms of sleepiness and cataplexy. *J. Neurosci.* 32, 12305–12311.
- Calik, M.W., 2017. Update on the treatment of narcolepsy: clinical efficacy of pitolisant. *Nat. Sci. Sleep* 9, 127–133.
- Chase, M.H., Soja, P.J., Morales, F.R., 1989. Evidence that glycine mediates the postsynaptic potentials that inhibit lumbar motoneurons during the atonia of active sleep. *J. Neurosci.* 9, 743–751.
- Chen, Z.K., Yuan, X.S., Dong, H., Wu, Y.F., Chen, G.H., He, M., Qu, W.M., Huang, Z.L., 2019. Whole-brain neural connectivity to lateral pontine tegmentum GABAergic neurons in mice. *Front. Neurosci.* 13, 375.
- Clement, O., Sapin, E., Berod, A., Fort, P., Luppi, P.H., 2011. Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep* 34, 419–423.
- Cox, J., Pinto, L., Dan, Y., 2016. Calcium imaging of sleep-wake related neuronal activity in the dorsal pons. *Nat. Commun.* 7, 10763.
- Cruz, H.G., Ivanova, T., Lunn, M.L., Stoffel, M., Slesinger, P.A., Luscher, C., 2004. Bidirectional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. *Nat. Neurosci.* 7, 153–159.
- Darwish, M., Kirby, M., Hellriegel, E.T., Robertson Jr., P., 2009. Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. *Clin. Drug Investig.* 29, 613–623.
- Dauvilliers, Y., Montplaisir, J., Molinari, N., Carlander, B., Ondze, B., Besset, A., Billiard, M., 2001. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology* 57, 2029–2033.
- Dauvilliers, Y., Bassetti, C., Lammers, G.J., Arnulf, I., Mayer, G., Rodenbeck, A., Leher, P., Ding, C.-L., Lecomte, J.-M., Schwartz, J.-C., 2013. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol.* 12, 1068–1075.
- de Almeida, C.M.O., Pachito, D.V., Sobreira-Neto, M.A., Tumas, V., Eckeli, A.L., 2018. Pharmacological treatment for REM sleep behavior disorder in Parkinson disease and related conditions: a scoping review. *J. Neurol. Sci.* 393, 63–68.
- Dement, W., Kleitman, N., 1957. The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. *J. Exp. Psychol.* 53, 339–346.
- Dunmyre, J.R., Mashour, G.A., Booth, V., 2014. Coupled flip-flop model for REM sleep regulation in the rat. *PLoS One* 9 e94481.
- el Mansari, M., Sakai, K., Jouvet, M., 1989. Unitary characteristics of presumptive cholinergic tegmental neurons during the sleep-waking cycle in freely moving cats. *Exp. Brain Res.* 76, 519–529.
- Elazar, Z., Berchanski, A., 2001. Glutamatergic-cholinergic synergistic interaction in the pontine reticular formation. Effects on cataplexy. *Naunyn-Schmiedeberg Arch. Pharmacol.* 363, 569–576.
- Erickson, E.T.M., Ferrari, L.L., Gompf, H.S., Anacleit, C., 2019. Differential role of pontomedullary glutamatergic neuronal populations in sleep-wake control. *Front. Neurosci.* 13, 755.
- Eugster, L., Bargiotas, P., Bassetti, C.L., Michael Schuepbach, W.M., 2016. Deep brain stimulation and sleep-wake functions in Parkinson's disease: a systematic review. *Parkinsonism Relat. Disord.* 32, 12–19.
- Fenik, V.B., Davies, R.O., Kubin, L., 2005. REM sleep-like atonia of hypoglossal (XII) motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am. J. Respir. Crit. Care Med.* 172, 1322–1330.
- Ford, B., Holmes, C.J., Mainville, L., Jones, B.E., 1995. GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. *J. Comp. Neurol.* 363, 177–196.
- Galbiati, A., Rinaldi, F., Giora, E., Ferini-Strambi, L., Marelli, S., 2015. Behavioural and cognitive-behavioural treatments of parasomnias. *Behav. Neurol.* 2015, 786928.
- Goutagny, R., Comte, J.C., Salvert, D., Gomeza, J., Yamada, M., Wess, J., Luppi, P.H., Fort, P., 2005. Paradoxical sleep in mice lacking M3 and M2/M4 muscarinic receptors. *Neuropsychobiology* 52, 140–146.
- Grace, K.P., Horner, R.L., 2015. Evaluating the evidence surrounding pontine cholinergic involvement in REM sleep generation. *Front. Neurol.* 6, 190.
- Grace, K.P., Vanstone, L.E., Horner, R.L., 2014. Endogenous cholinergic input to the pontine REM sleep generator is not required for REM sleep to occur. *J. Neurosci.* 34, 14198–14209.
- Greene, R.W., Gerber, U., McCarley, R.W., 1989. Cholinergic activation of medial pontine reticular formation neurons in vitro. *Brain Res.* 476, 154–159.

- Group, X.I.S., 2005. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J. Clin. Sleep Med.* 1, 391–397.
- Hanriot, L., Camargo, N., Courau, A.C., Leger, L., Luppi, P.H., Peyron, C., 2007. Characterization of the melanin-concentrating hormone neurons activated during paradoxical sleep hypersomnia in rats. *J. Comp. Neurol.* 505, 147–157.
- Hayashi, Y., Kashiwagi, M., Yasuda, K., Ando, R., Kanuka, M., Sakai, K., Itohara, S., 2015. Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice. *Science* 350, 957–961.
- Hendricks, J.C., Morrison, A.R., Mann, G.L., 1982. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. *Brain Res.* 239, 81–105.
- Henriksen, S.J., Jacobs, B.L., Dement, W.C., 1972. Dependence of REM sleep PGO waves on cholinergic mechanisms. *Brain Res.* 48, 412–416.
- Hobson, J.A., McCarley, R.W., Wyzinski, P.W., 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science* 189, 55–58.
- Holmes, C.J., Jones, B.E., 1994. Importance of cholinergic, GABAergic, serotonergic and other neurons in the medial medullary reticular formation for sleep-wake states studied by cytotoxic lesions in the cat. *Neuroscience* 62, 1179–1200.
- Hoshino, K., Pompeiano, O., 1976. Selective discharge of pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat. *Arch. Ital. Biol.* 114, 244–247.
- Huang, Y.S., Guillemainault, C., 2009. Narcolepsy: action of two gamma-aminobutyric acid type B agonists, baclofen and sodium oxybate. *Pediatr. Neurol.* 41, 9–16.
- Hublin, C., Partinen, M., Heinonen, E.H., Puukka, P., Salmi, T., 1994. Selegiline in the treatment of narcolepsy. *Neurology* 44, 2095–2101.
- Iranzo, A., Tolosa, E., Gelpi, E., Molinuevo, J.L., Valldeoriola, F., Serradell, M., Sanchez-Valle, R., Vilaseca, I., Lomena, F., Vilas, D., Llado, A., Gaig, C., Santamaria, J., 2013. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol.* 12, 443–453.
- Irukayama-Tomobe, Y., Yanagisawa, M., 2018. [Development of a therapeutic drug for narcolepsy]. *Brain Nerve* 70, 1255–1263.
- Izawa, S., Chowdhury, S., Miyazaki, T., Mukai, Y., Ono, D., Inoue, R., Ohmura, Y., Mizoguchi, H., Kimura, K., Yoshioka, M., Terao, A., Kilduff, T.S., Yamanaka, A., 2019. REM sleep-active MCH neurons are involved in forgetting hippocampus-dependent memories. *Science* 365, 1308–1313.
- Jacobs, B.L., Henriksen, S.J., Dement, W.C., 1972. Neurochemical bases of the PGO wave. *Brain Res.* 48, 406–411.
- Jones, B.E., 1991. Paradoxical sleep and its chemical/structural substrates in the brain. *Neuroscience* 40, 637–656.
- Jones, B.E., Harper, S.T., Halaris, A.E., 1977. Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat. *Brain Res.* 124, 473–496.
- Jouvet, M., 1962. [Research on the neural structures and responsible mechanisms in different phases of physiological sleep]. *Arch. Ital. Biol.* 100, 125–206.
- Kallweit, U., Bassetti, C.L., 2017. Pharmacological management of narcolepsy with and without cataplexy. *Expert Opin. Pharmacother.* 18, 809–817.
- Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J., Sagi, D., 1994. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science* 265, 679–682.
- Kashiwagi, K., Nomura, T., Maeda, T., Tsuboi, Y., Mishima, T., Takigawa, H., Nakashima, K., 2016. Beneficial effects of ramelteon on rapid eye movement sleep behavior disorder associated with Parkinson's disease - results of a multicenter open trial. *Intern. Med.* 55, 231–236.
- Kashiwagi, M., Kanuka, M., Tatsuzawa, C., Suzuki, H., Morita, M., Tanaka, K., Kawano, T., Shin, J.W., Suzuki, H., Itohara, S., Yanagisawa, M., Hayashi, Y., 2020. Widely distributed neurotensinergic neurons in the brainstem regulate NREM sleep in mice. *Curr. Biol.* 30 (1002–1010), e1004.
- Kayama, Y., Ohta, M., Jodo, E., 1992. Firing of 'possibly' cholinergic neurons in the rat laterodorsal tegmental nucleus during sleep and wakefulness. *Brain Res.* 569, 210–220.
- Krenzer, M., Anacleit, C., Vetrivelan, R., Wang, N., Vong, L., Lowell, B.B., Fuller, P.M., Lu, J., 2011. Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PLoS One* 6 e24998.
- Kubin, L., 2001. Carbachol models of REM sleep: recent developments and new directions. *Arch. Ital. Biol.* 139, 147–168.
- Kumru, H., Iranzo, A., Carrasco, E., Valldeoriola, F., Marti, M.J., Santamaria, J., Tolosa, E., 2008. Lack of effects of pramipexole on REM sleep behavior disorder in Parkinson disease. *Sleep* 31, 1418–1421.
- Kunz, D., Bes, F., 1999. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov. Disord.* 14, 507–511.
- Lai, Y.Y., Hsieh, K.C., Nguyen, D., Peever, J., Siegel, J.M., 2008. Neurotoxic lesions at the ventral mesopontine junction change sleep time and muscle activity during sleep: an animal model of motor disorders in sleep. *Neuroscience* 154, 431–443.
- Lauriello, J., Kenny, W.M., Sutton, L., Golshan, S., Ruiz, C., Kelsoe, J., Rapaport, M., Gillin, J.C., 1993. The cholinergic REM sleep induction test with pilocarpine in mildly depressed patients and normal controls. *Biol. Psychiatry* 33, 33–39.
- Lee, M.G., Manns, I.D., Alonso, A., Jones, B.E., 2004. Sleep-wake related discharge properties of basal forebrain neurons recorded with micropipettes in head-fixed rats. *J. Neurophysiol.* 92, 1182–1198.
- Lee, M.G., Hassani, O.K., Alonso, A., Jones, B.E., 2005. Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. *J. Neurosci.* 25, 4365–4369.
- Li, X., Rainnie, D.G., McCarley, R.W., Greene, R.W., 1998. Presynaptic nicotinic receptors facilitate monoaminergic transmission. *J. Neurosci.* 18, 1904–1912.
- Liblaur, R.S., Vassalli, A., Seifinejad, A., Tafti, M., 2015. Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. *Lancet Neurol.* 14, 318–328.
- Liu, D., Dan, Y., 2019. A motor theory of sleep-wake control: arousal-action circuit. *Annu. Rev. Neurosci.*
- Liu, M., Blanco-Centurion, C., Konadhode, R., Begum, S., Pelluru, D., Gerashchenko, D., Sakurai, T., Yanagisawa, M., van den Pol, A.N., Shiromani, P.J., 2011. Orexin gene transfer into zona incerta neurons suppresses muscle paralysis in narcoleptic mice. *J. Neurosci.* 31, 6028–6040.
- Lu, J., Sherman, D., Devor, M., Saper, C.B., 2006. A putative flip-flop switch for control of REM sleep. *Nature* 441, 589–594.
- Luppi, P.H., Clement, O., Sapin, E., Gervasoni, D., Peyron, C., Leger, L., Salvert, D., Fort, P., 2011. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Med. Rev.* 15, 153–163.
- Luppi, P.H., Clement, O., Fort, P., 2013. Paradoxical (REM) sleep genesis by the brainstem is under hypothalamic control. *Curr. Opin. Neurobiol.* 23, 786–792.
- Lydic, R., McCarley, R.W., Hobson, J.A., 1983. The time-course of dorsal raphe discharge, PGO waves, and muscle tone averaged across multiple sleep cycles. *Brain Res.* 274, 365–370.
- Magherini, P.C., Pompeiano, O., Thoden, U., 1971. The neurochemical basis of REM sleep: a cholinergic mechanism responsible for rhythmic activation of the vestibulo-oculomotor system. *Brain Res.* 35, 565–569.
- Magoun, H.W., Rhines, R., 1946. An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.* 9, 165–171.
- Maloney, K.J., Mainville, L., Jones, B.E., 1999. Differential c-Fos expression in cholinergic, monoaminergic, and GABAergic cell groups of the pontomesencephalic tegmentum after paradoxical sleep deprivation and recovery. *J. Neurosci.* 19, 3057–3072.
- Maloney, K.J., Mainville, L., Jones, B.E., 2000. c-Fos expression in GABAergic, serotonergic, and other neurons of the pontomesencephalic tegmentum after paradoxical sleep deprivation and recovery. *J. Neurosci.* 20, 4669–4679.
- Marquez-Ruiz, J., Escudero, M., 2008. Tonic and phasic phenomena underlying eye movements during sleep in the cat. *J. Physiol.* 586, 3461–3477.
- Massaquoi, S.G., McCarley, R.W., 1992. Extension of the limit cycle reciprocal interaction model of REM cycle control. An integrated sleep control model. *J. Sleep Res.* 1, 138–143.
- McCarley, R.W., Hobson, J.A., 1975. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science* 189, 58–60.
- McCarley, R.W., Massaquoi, S.G., 1986. A limit cycle mathematical model of the REM sleep oscillator system. *Am. J. Physiol.* 251, R1011–1029.
- McGinty, D.J., Harper, R.M., 1976. Dorsal raphe neurons: depression of firing during sleep in cats. *Brain Res.* 101, 569–575.
- McGrane, I.R., Leung, J.G., St Louis, E.K., Boeve, B.F., 2015. Melatonin therapy for REM sleep behavior disorder: a critical review of evidence. *Sleep Med.* 16, 19–26.
- Medicine, A.Ao.S., 2014. International Classification of Sleep Disorders, 3rd ed. American Academy of Sleep Medicine, Darien, IL.
- Mefford, I.N., Baker, T.L., Boehme, R., Foutz, A.S., Ciaranello, R.D., Barchas, J.D., Dement, W.C., 1983. Narcolepsy: biogenic amine deficits in an animal model. *Science* 220, 629–632.
- Mignot, E.J., 2012. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. *Neurotherapeutics* 9, 739–752.
- Mitani, A., Ito, K., Hallanger, A.E., Wainer, B.H., Kataoka, K., McCarley, R.W., 1988. Cholinergic projections from the laterodorsal and pedunculopontine tegmental nuclei to the pontine gigantocellular tegmental field in the cat. *Brain Res.* 451, 397–402.
- Monti, A., Medigue, C., Nedelcoux, H., Escourrou, P., 2002. Autonomic control of the cardiovascular system during sleep in normal subjects. *Eur. J. Appl. Physiol.* 87, 174–181.
- Mouret, J., Coindet, J., 1980. Polygraphic evidence against a critical role of the raphe nuclei in sleep in the rat. *Brain Res.* 186, 273–287.
- Nagahara, T., Saitoh, T., Kutsumura, N., Irukayama-Tomobe, Y., Ogawa, Y., Kuroda, D., Gouda, H., Kumagai, H., Fujii, H., Yanagisawa, M., Nagase, H., 2015. Design and synthesis of non-peptide, selective orexin receptor 2 agonists. *J. Med. Chem.* 58, 7931–7937.
- Negoescu, R.M., Csiki, I.E., 1989. Autonomic control of the heart in some vagal maneuvers and normal sleep. *Physiologie* 26, 39–49.
- Nishino, S., Ripley, B., Overeem, S., Lammers, G.J., Mignot, E., 2000. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 355, 39–40.
- Nitz, D., Siegel, J., 1997a. GABA release in the dorsal raphe nucleus: role in the control of REM sleep. *Am. J. Physiol.* 273, R451–455.
- Nitz, D., Siegel, J.M., 1997b. GABA release in the locus coeruleus as a function of sleep/wake state. *Neuroscience* 78, 795–801.
- Ohayon, M.M., Priest, R.G., Zulley, J., Smirne, S., Paiva, T., 2002. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology* 58, 1826–1833.
- Onoe, H., Sakai, K., 1995. Kainate receptors: a novel mechanism in paradoxical (REM) sleep generation. *Neuroreport* 6, 353–356.
- Peever, J., Fuller, P.M., 2017. The biology of REM sleep. *Curr. Biol.* 27, R1237–R1248.
- Peever, J., Luppi, P.H., Montplaisir, J., 2014. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci.* 37, 279–288.
- Pickel, V.M., Segal, M., Bloom, F.E., 1974. A radioautographic study of the efferent pathways of the nucleus locus coeruleus. *J. Comp. Neurol.* 155, 15–42.
- Pompeiano, O., 1975. The control of posture and movements during REM sleep: neurophysiological and neurochemical mechanisms. *Acta Astronaut.* 2, 225–239.

- Rauniar, G.P., Gitanjali, B., Shashindran, C., 1998. Comparative effects of hyoscine butylbromide and atropine sulphate on sleep architecture in healthy human volunteers. *Indian J. Physiol. Pharmacol.* 42, 395–400.
- Reading, P.J., 2019. Update on narcolepsy. *J. Neurol.* 266, 1809–1815.
- Reid, M.S., Tafti, M., Nishino, S., Siegel, J.M., Dement, W.C., Mignot, E., 1994. Cholinergic regulation of cataplexy in canine narcolepsy in the pontine reticular formation is mediated by M2 muscarinic receptors. *Sleep* 17, 424–435.
- Roffwarg, H.P., Muzio, J.N., Dement, W.C., 1966. Ontogenetic development of the human sleep-dream cycle. *Science* 152, 604–619.
- Sakai, K., Koyama, Y., 1996. Are there cholinergic and non-cholinergic paradoxical sleep-on neurons in the pons? *Neuroreport* 7, 2449–2453.
- Sakai, K., Crochet, S., Onoe, H., 2001. Pontine structures and mechanisms involved in the generation of paradoxical (REM) sleep. *Arch. Ital. Biol.* 139, 93–107.
- Sanford, L.D., Tang, X., Xiao, J., Ross, R.J., Morrison, A.R., 2003. GABAergic regulation of REM sleep in reticularis pontis oralis and caudalis in rats. *J. Neurophysiol.* 90, 938–945.
- Sapin, E., Lapray, D., Berod, A., Goutagny, R., Leger, L., Ravassard, P., Clement, O., Hanriot, L., Fort, P., Luppi, P.H., 2009. Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. *PLoS One* 4 e4272.
- Sapin, E., Berod, A., Leger, L., Herman, P.A., Luppi, P.H., Peyron, C., 2010. A very large number of GABAergic neurons are activated in the tuberal hypothalamus during paradoxical (REM) sleep hypersomnia. *PLoS One* 5 e11766.
- Sateia, M.J., 2014. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 146, 1387–1394.
- Scammell, T.E., 2015. Narcolepsy. *N. Engl. J. Med.* 373, 2654–2662.
- Schenck, C.H., Hurwitz, T.D., Mahowald, M.W., 1993. Symposium: normal and abnormal REM sleep regulation: REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. *J. Sleep Res.* 2, 224–231.
- Schenck, C.H., Boeve, B.F., Mahowald, M.W., 2013. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med.* 14, 744–748.
- Schenkel, E., Siegel, J.M., 1989. REM sleep without atonia after lesions of the medial medulla. *Neurosci. Lett.* 98, 159–165.
- Scherfler, C., Frauscher, B., Schocke, M., Iranzo, A., Gschliesser, V., Seppe, K., Santamaria, J., Tolosa, E., Hogl, B., Poewe, W., 2011. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. *Ann. Neurol.* 69, 400–407.
- Schmidt, M.H., Koshal, V.B., Schmidt, H.S., 2006. Use of pramipexole in REM sleep behavior disorder: results from a case series. *Sleep Med.* 7, 418–423.
- Semba, K., Fibiger, H.C., 1992. Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. *J. Comp. Neurol.* 323, 387–410.
- Shin, J., Kim, D., Bianchi, R., Wong, R.K., Shin, H.S., 2005. Genetic dissection of theta rhythm heterogeneity in mice. *Proc. Natl. Acad. Sci. U. S. A.* 102, 18165–18170.
- Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, H.M., Pettigrew, J.D., 1998. Monotremes and the evolution of rapid eye movement sleep. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 353, 1147–1157.
- Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, H.M., Shalita, T., Pettigrew, J.D., 1999. Sleep in the platypus. *Neuroscience* 91, 391–400.
- Steriade, M., Pare, D., Datta, S., Oakson, G., Curro Dossi, R., 1990. Different cellular types in mesopontine cholinergic nuclei related to ponto-geniculo-occipital waves. *J. Neurosci.* 10, 2560–2579.
- Stevens, D.R., Birmstiel, S., Gerber, U., McCarley, R.W., Greene, R.W., 1993. Nicotinic depolarizations of rat medial pontine reticular formation neurons studied in vitro. *Neuroscience* 57, 419–424.
- Takahashi, K., Lin, J.S., Sakai, K., 2008. Neuronal activity of orexin and non-orexin waking-active neurons during wake-sleep states in the mouse. *Neuroscience* 153, 860–870.
- Takahashi, K., Lin, J.S., Sakai, K., 2009. Characterization and mapping of sleep-waking specific neurons in the basal forebrain and preoptic hypothalamus in mice. *Neuroscience* 161, 269–292.
- Thakkar, M., Portas, C., McCarley, R.W., 1996. Chronic low-amplitude electrical stimulation of the laterodorsal tegmental nucleus of freely moving cats increases REM sleep. *Brain Res.* 723, 223–227.
- Thakkar, M.M., Strecker, R.E., McCarley, R.W., 1998. Behavioral state control through differential serotonergic inhibition in the mesopontine cholinergic nuclei: a simultaneous unit recording and microdialysis study. *J. Neurosci.* 18, 5490–5497.
- Thannickal, T.C., Moore, R.Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M., Siegel, J.M., 2000. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27, 469–474.
- Thorpy, M.J., 2015. Update on therapy for narcolepsy. *Curr. Treat. Options Neurol.* 17, 347.
- Thorpy, M.J., Dauvilliers, Y., 2015. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med.* 16, 9–18.
- Tinuper, P., Provini, F., Bisulli, F., Vignatelli, L., Plazzi, G., Vetrugno, R., Montagna, P., Lugaresi, E., 2007. Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep. *Sleep Med. Rev.* 11, 255–267.
- Torontali, Z.A., Fraigne, J.J., Sanghera, P., Horner, R., Peever, J., 2019. The sublaterodorsal tegmental nucleus functions to couple brain state and motor activity during REM sleep and wakefulness. *Curr. Biol.* 29 (3803–3813) e3805.
- Valencia Garcia, S., Libourel, P.A., Lazarus, M., Grassi, D., Luppi, P.H., Fort, P., 2017. Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder. *Brain* 140, 414–428.
- Vanni-Mercier, G., Sakai, K., Lin, J.S., Jouvet, M., 1989. Mapping of cholinergic brainstem structures responsible for the generation of paradoxical sleep in the cat. *Arch. Ital. Biol.* 127, 133–164.
- Verret, L., Leger, L., Fort, P., Luppi, P.H., 2005. Cholinergic and noncholinergic brainstem neurons expressing Fos after paradoxical (REM) sleep deprivation and recovery. *Eur. J. Neurosci.* 21, 2488–2504.
- Verret, L., Fort, P., Gervasoni, D., Leger, L., Luppi, P.H., 2006. Localization of the neurons active during paradoxical (REM) sleep and projecting to the locus coeruleus noradrenergic neurons in the rat. *J. Comp. Neurol.* 495, 573–586.
- Vetrivelan, R., Fuller, P.M., Tong, Q., Lu, J., 2009. Medullary circuitry regulating rapid eye movement sleep and motor atonia. *J. Neurosci.* 29, 9361–9369.
- Walsh, J.K., Hall-Porter, J.M., Griffin, K.S., Dodson, E.R., Forst, E.H., Curry, D.T., Eisenstein, R.D., Schweitzer, P.K., 2010. Enhancing slow wave sleep with sodium oxybate reduces the behavioral and physiological impact of sleep loss. *Sleep* 33, 1217–1225.
- Wang, Y.Q., Tu, Z.C., Xu, X.Y., Li, R., Qu, W.M., Urade, Y., Huang, Z.L., 2012. Acute administration of fluoxetine normalizes rapid eye movement sleep abnormality, but not depressive behaviors in olfactory bulbectomized rats. *J. Neurochem.* 120, 314–324.
- Wang, Y.Q., Li, R., Wang, D.R., Cherasse, Y., Zhang, Z., Zhang, M.Q., Lavielle, O., McEown, K., Schiffmann, S.N., de Kerchove d'Exaerde, A., Qu, W.M., Lazarus, M., Huang, Z.L., 2017. Adenosine A2A receptors in the olfactory bulb suppress rapid eye movement sleep in rodents. *Brain Struct. Funct.* 222, 1351–1366.
- Weber, F., Chung, S., Beier, K.T., Xu, M., Luo, L., Dan, Y., 2015. Control of REM sleep by ventral medulla GABAergic neurons. *Nature* 526, 435–438.
- Williams, J.A., Reiner, P.B., 1993. Noradrenergic hyperpolarizes identified rat mesopontine cholinergic neurons in vitro. *J. Neurosci.* 13, 3878–3883.
- Willie, J.T., Renthal, W., Chemelli, R.M., Miller, M.S., Scammell, T.E., Yanagisawa, M., Sinton, C.M., 2005. Modafinil more effectively induces wakefulness in orexin-null mice than in wild-type littermates. *Neuroscience* 130, 983–995.
- Wisor, J., 2013. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. *Front. Neurol.* 4, 139.
- Xi, M.C., Morales, F.R., Chase, M.H., 1999. Evidence that wakefulness and REM sleep are controlled by a GABAergic pontine mechanism. *J. Neurophysiol.* 82, 2015–2019.
- Xi, M.C., Morales, F.R., Chase, M.H., 2001. The motor inhibitory system operating during active sleep is tonically suppressed by GABAergic mechanisms during other states. *J. Neurophysiol.* 86, 1908–1915.
- Yang, J., Gao, J., 2019. Solriamfetol for the treatment of excessive daytime sleepiness associated with narcolepsy. *Expert Rev. Clin. Pharmacol.* 1–6.
- Ylikoski, A., Martikainen, K., Partinen, M., 2014. Parasomnias and isolated sleep symptoms in Parkinson's disease: a questionnaire study on 661 patients. *J. Neurol. Sci.* 346, 204–208.
- Yoss, R.E., Daly, D.D., 1957. Criteria for the diagnosis of the narcoleptic syndrome. *Proc. Staff Meet. Mayo Clin.* 32, 320–328.
- Zhong, P., Zhang, Z., Barger, Z., Ma, C., Liu, D., Ding, X., Dan, Y., 2019. Control of non-REM sleep by midbrain neurotensinergic neurons. *Neuron* 104 (795–809), e796.