Progress in Neurobiology xxx (xxxx) 102106

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

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

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ARTICLE INFO

*Keywords:*
Rapid eye movement sleep
REM sleep-regulatory model
REM sleep behavior disorder
Narcolepsy

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 by noradrenergic antidepressants. 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 "para-

*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, sublaterodorsal tegmental nucleus; , ; SubC, subcoeruleus nucleus; vlPAG, ventrolateral periaqueductal gray matter; vMM, ventromedial medulla

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https://doi.org/10.1016/j.pneurobio.2021.102106
Received 11 November 2020; Received in revised form 25 April 2021; Accepted 9 June 2021
0301-0082/

doxical 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 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 defacilitation 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 serotoninergic 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 activatee 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., decreased REM sleep latency and an increased 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 (vlPAG) 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 vlPAG 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 laterodorsal tegmental nucleus-SLD and vlPAG-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 vlPAG/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., vlPAG 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 vlPAG 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 vlPAG and LPT also negatively regulate REM sleep (Kashiwagi et al., 2020; Zhong et al., 2019). In support of this model, microinjection of bicuculine 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 vlPAG and LPT, while the projections from the vlPAG 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 vlPAG 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). Chemogenetic 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) hypnogogic 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 Fig. 1. 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).

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).

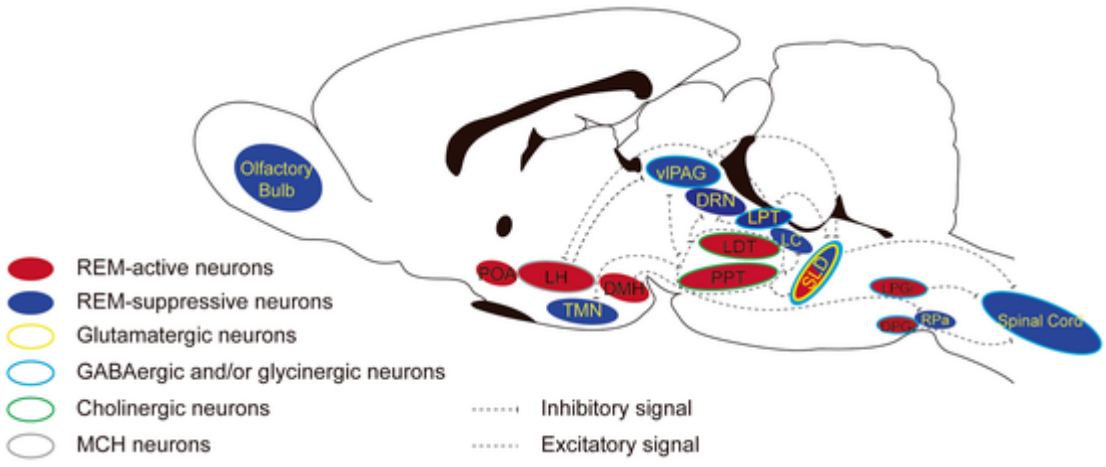


**Fig. 1.** Summary of REM sleep networks. SLD glutamatergic neurons are critical in the regulation of REM sleep. For REM sleep maintenance and muscle atonia, cholinergic neurons in the LDT/PPT are important, as are GABAergic neurons in the LPGi, DPGi, vlPAG, LPT, and spinal cord. The dashed lines in 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.

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, parexetine, 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 (Alatriste-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 hypnogogic 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 anticataplectic 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 $H_3$ 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, phytocannabinoids, 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.

## Acknowledgements

This study was supported in part by grants-in-aid for scientific research from the National Key Research and Development Program of China (2020YFC2005300), National Natural Science Foundation of China (82020108014, 81871037, 32070984, 31871072, and 82071491), Shanghai Municipal Science and Technology Major Project (2018SHZDZX01) and ZJLab, Program for Shanghai Outstanding Academic Leaders (to Z.-L.H), Shanghai Science and Technology Innovation Action Project (201409001800), and a key laboratory program of the Education Commission of Shanghai Municipality (ZDSYS14005).

## 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.

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