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Perspectives on the rapid eye movement sleep switch in rapid eye movement sleep behavior disorder

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Abstract

Rapid eye movement (REM) sleep in mammals is associated with wakelike cortical and hippocampal activation and concurrent postural muscle atonia. Research during the past 5 decades has revealed the details of the neural circuitry regulating REM sleep and muscle atonia during this state. REM-active glutamatergic neurons in the sublaterodorsal nucleus (SLD) of the dorsal pons are critical for generation for REM sleep atonia. Descending projections from SLD glutamatergic neurons activate inhibitory premotor neurons in the ventromedial medulla (VMM) and in the spinal cord to antagonize the glutamatergic supraspinal inputs on the motor neurons during REM sleep. REM sleep behavior disorder (RBD) consists of simple behaviors (i.e., twitching, jerking) and complex behaviors (i.e., defensive behavior, talking). Animal research has led to the hypothesis that complex behaviors in RBD are due to SLD pathology, while simple behaviors of RBD may be due to less severe SLD pathology or dysfunction of the VMM, ventral pons, or spinal cord.

Keywords

Neural circuitry; Brainstem; Atonia; Phasic regulation; Tonic regulation

1. Introduction

Rapid eye movement (REM) sleep is a unique state in the sleep–wake cycle characterized by cortical and hippocampal activation [1–5] and concurrent loss of muscle tone (atonia) in somatic musculature. Because the electroencephalogram (EEG) during REM sleep resembles EEG during wakefulness, which is low voltage and high frequency in the cerebral cortex with (5–9 Hz) waves in the hippocampus, REM sleep also is called paradoxical sleep or active sleep. Apart from cortical activation and muscle atonia, REM sleep is characterized by other cardinal signs, which can be broadly classified into tonic components that are present throughout the REM sleep episodes and phasic components that appear intermittently during REM sleep. Tonic components include activated EEG, muscle atonia, and loss of thermoregulation (poikilothermia). Phasic components include muscle twitches in the spinal cord and cranial musculature occurring intermittently against the background muscle atonia; REMs; ponto–geniculo–occipital (PGO) waves; and irregularities in heart rate, blood pressure, and breathing. We focus our discussion on the tonic and phasic muscle

Conflict of interest

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events during REM sleep, the neural circuitry involved in their generation and maintenance, and their clinical relevance in REM sleep behavior disorder (RBD).

REM sleep is characterized by sustained low muscle tone with no detectable movements occurring in most of the somatic musculature except the inner ear muscles and diaphragm. However, smaller muscles such as the cranial muscles of the eyes, ears, and jaw, as well as muscles of the limb extremities display notable phasic movements against a background of overall low muscle tone during REM sleep; larger postural muscles rarely exhibit this phasic activity. In patients with neurodegenerative diseases such as Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB), incomplete muscle atonia may occur resulting in overt motor behaviors during REM sleep. Schenck et al. [6] first named this parasomnia (RBD). By 1996 they reported that 38% of their original cohort of 29 patients had developed parkinsonism [7], and by 20 years after diagnosis 81% of that cohort now had parkinsonism [8]. Subsequent studies have shown that approximately half of patients with idiopathic RBD (iRBD) develop a synucleinopathy (PD, DLB, or MSA) by approximately 12 years after RBD diagnosis [9–11]. On the other hand, approximately 60% of PD patients do not have RBD [12], and interestingly parkinsonism may be reduced in PD-RBD subjects [13].

RBD has a wide spectrum of overt symptoms, ranging from jerking, twitching, shouting, and screaming, as well as defensive punching and escape behaviors that may cause some patients to injure themselves or others. These behaviors can be divided into simple behaviors (e.g., twitching) and complex behaviors (e.g., defensive punching or talking). However, other normal phasic features occurring in REM sleep such as REMs and heart rate appear to be unaffected in iRBD patients, indicating that RBD is caused by dysfunction of the specific inhibitory circuit controlling postural motor neurons. Although the neuropathology of RBD and mechanisms are far from clear, basic research investigating the neural circuitry of REM sleep and muscle atonia in animals has shed light on the potential pathways of which dysfunction may cause RBD [1,2,14–18].

2. Motor control during REM sleep

When motor activity is present in RBD, it manifests as simple and complex behaviors. Although brief bursts of electromyogram (EMG) activation and muscle twitches in REM sleep are viewed as phasic, it is difficult to know how to classify more complex behavioral events, such as a cat chasing a phantom mouse or a human patient with RBD fighting off an assailant. It is possible that the difference between tonic and phasic may be more quantitative than qualitative, depending on the nature of the motor behaviors breaking through the REM atonia when excitatory drive is sufficient to exceed inhibitory input. It has been determined from the classic work by Chase and Morales [19] that spinal motor neurons are inhibited by barrages of glycinergic inhibitory postsynaptic potentials during REM sleep [19]. In neurophysiologic terms, inputs from REM atonia circuits activate glycinergic and GABAergic premotor neurons that inhibit motor neurons. Importantly, the phasic movements and EMG particularly are disinhibited in humans with RBD. Thus RBD results more from failure of the suppression of phasic activity of postural muscles than from dysfunction of tonic control.

In the last several decades, researchers have begun elucidating the neural inputs that drive suppression of phasic activity. In 1959 Jouvet and Michel [20] first reported that electrolytic lesions of the subcoeruleus region (SC) (ventral to the locus coeruleus) in the dorsal pons resulted in loss of muscle atonia during REM sleep in cats. These cats displayed disinhibited behaviors ranging from simple twitching and jerking to various complex motor behaviors such as chasing a phantom mouse during REM sleep. This finding was confirmed and

further explored by Henley and Morrison [21] in 1974 and Hendricks et al. [22] in 1982. However, lesions in this location in rats did not consistently induce an RBD-like phenotype [23,24]. It was later revealed that the neurons critical for the generation of muscle atonia in rats are located slightly rostral to this region, specifically ventral to the caudal part of the laterodorsal tegmental nucleus (cLDT) and hence named the sublateralodorsal tegmental nucleus (SLD) [16,25,26]. Local stimulation of this region by a glutamate agonist or GABA antagonist but not a cholinergic agonist produced REM sleep with cortical activation and atonia in head-fixed rats [26], suggesting that the SLD may be critical in generating desynchronized EEG and muscle atonia. The SLD contains reticulo-spinal glutamatergic neurons that directly project to inhibitory interneurons in lamina VII of the spinal cord and to the ventromedial medulla (VMM) at the level of inferior olive, which also is called the supraolivary medulla (SOM) [16,27]. In turn the SLD itself can be defined by the distribution of neurons in that region which were labeled by retrograde tracing from the spinal cord. Excitotoxic lesions confined to the SLD resulted in a RBD-like phenotype in rats [16] exhibiting simple and complex behaviors, including jerking, twitching, walking, running, and leaping during REM sleep, similar to the behavioral phenotypes observed in humans with RBD or in cats with subcoeruleus lesions [16]. We subsequently identified the neuroanatomic locus of the SLD in mice by retrograde tracing from the spinal ventral horn. The location of these neurons in mice was similar to the SLD in rats. We further showed that focal elimination of glutamate transmission from the SLD neurons in mice produced an RBD-like phenotype [14]. These findings confirmed that glutamatergic neurons in the SLD are critical for generating muscle atonia during REM sleep.

Electric stimulation in the VMM (or SOM) in decerebrate animals caused a decrease in muscle tone, as did injecting the same sites with quisqualate, a 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptor agonist [28]. On the other hand, the injection of *N*-methyl-D-aspartate agonists at these sites produced increased muscle tone [29,30], suggesting that the VMM contains a complex combination of cell populations that bear different classes of glutamate receptors; some of the receptors increase muscle tone and some of them decrease muscle tone. Furthermore, there are GABA-glycinergic neurons in the VMM projecting to the spinal cord motor neurons which are activated during REM sleep [31]. Importantly cell-body lesions of the VMM resulted in the occurrence of simple behaviors, sporadic phasic jerking, and twitching movements during REM sleep in both cats and rats [27,32]. However, in contrast to SLD lesions, complex behaviors are not observed. Animals with VMM lesions sometimes also demonstrated abrupt acceleration into the cage walls at the end of REM sleep, which also is seen in SLD lesions, suggesting that this particular behavior is due to loss of control along a SLD to VMM to spinal cord pathway. Most of the movements seen in VMM-lesioned rats were rapid and jerky, particularly in the hind limbs and tail [27]. To understand the neurotransmitters in the VMM neurons involved in muscle atonia, we focally eliminated glutamate or GABA/glycine neurotransmission from the VMM neurons and found glutamate elimination produced more prominent phasic activity in the neck EMG than was produced by elimination of GABA/glycine neurotransmission. Because simultaneous video recordings were not performed, the behaviors associated with this phasic activity during REM sleep in these mice are unclear.

These studies collectively indicate that VMM neurons partially mediate SLD control on atonia. On the other hand, SLD also has direct projections to the lamina VII in the spinal cord where GABA/glycinergic interneurons are located, and genetic elimination of GABA/glycinergic neurotransmission from the spinal cord ventral horn at the C3 to C4 level have resulted in brief twitching and jerking movements mostly in the upper and occasionally lower body extremities (including tail movements) in mice [14]. Other regions also likely contribute to the control of REM sleep atonia and also to the underlying pathology of RBD. For example, Lai et al. [33] have demonstrated that lesions of the ventral mesopontine

junction (VMPJ) in cats induced periodic leg movements (simple behaviors) during REM sleep. The authors proposed that the VMPJ may regulate atonia via the VMM. In addition to GABA/glycinergic neurotransmission, monoaminergic, orexinergic, and melanin-concentrating hormone neurons also may play a role in REM atonia either by their direct projections to the spinal cord or by acting on the ventrolateral periaqueductal gray matter (vlPAG)/lateral pontine tegmentum (LPT), the SLD, or the VMM neurons [1–3,17,34–38]. In summary, animal research indicates that the SLD and VMM are critical nodes of REM atonia control, and SLD lesions capture the full phenotype of RBD, while lesions of inputs to the VMM only produce the simple behaviors of RBD.

3. Phasic REM sleep

The original control of phasic REM sleep may come from the phasic REM-active neurons, located in the dorsal pontine tegmentum, including the pedunculo pontine tegmental nucleus (PPT), laterodorsal tegmental nucleus (LDT), and SLD [39–42]. For example, PGO waves, perhaps the most studied phasic event of REM sleep, are an electrical field identified in the periparabrachial area, thalamic lateral geniculate nucleus, and visual cortex in cats [43]. Because this electrical activity in rats mostly is confined to the dorsal pons, these pulses are known as P waves [43]. PGO waves can be triggered with a short latency by the cholinergic agonist carbachol in the caudal peribrachial area in cats [43,44]. In rats, the “hot spot” for P-wave induction is near the SLD [43]. It is now clear that phasic firing patterns during REM sleep are not confined to PGO waves but also are seen in many sites, including the subthalamic nucleus of the basal ganglia [47], the hippocampus, and the motor cortex [48]. We postulate that phasic activity from cLDT–SLD neurons, via the LDT–PPT–precoeruleus–parabrachial (PC–PB), is transferred to many sites in the forebrain and brainstem (Fig. 1B).

In cats electrolytic lesions of the PPT but not the LDT or subcoeruleus area reduce the phasic activity of eye movements and lateral geniculate nucleus firing of PGO waves [49]. Although this study could not determine the neurotransmitters (cholinergic neurons vs glutamatergic neurons) involved in this process, it does demonstrate that the PPT and surrounding regions contain the phasic eye movement generators. Glutamate has been shown to be responsible for driving cranial and spinal motor neurons that cause phasic twitches in these muscles [19,50]. Our recent findings revealed that glutamatergic neurons in the rostral parvocellular reticular formation (rPCrT) are critical for phasic masseter activity during REM sleep [51]. Specific elimination of glutamate neurotransmission from the rPCrT neurons resulted in the loss of phasic twitches in the masseter muscle but did not affect REMs during REM sleep. We hypothesize that the neural circuit regulating phasic activity of the masseter is phasic and REM-on neurons in the cLDT–SLD that activate the PC–PB–PPT–LDT in which glutamatergic and cholinergic neurons stimulate the cerebral cortex via massive projections, which in turn innervate the rPCrT to generate Mo5 phasic activity. The PC–PB projections to the preoptic area or paraventricular hypothalamic nucleus that activate the spinal cord sympathetic system also regulate phasic autonomic activity, such as heart rate and REM sleep penile tumescence (Fig. 1B). In line with these models, humans in a vegetative state who have little or no cortical activation during sleep cycles have greatly reduced phasic eye movements in REM sleep [52] but have intact REM sleep associated erections [53]. Because lesions in the SLD had no effects on the phasic masseter activity (EMG quantification) during REM sleep [51], we hypothesize that the SLD is not the generator of this phasic activity (Fig. 1B). Rather the SLD specifically functions to antagonize the phasic activity of postural muscles of complex behaviors driven by the motor cortex and simple behaviors controlled by brainstem–spinal cord circuit (Fig. 1B).

4. REM sleep switch

Early studies employing transections at different levels of the neuraxis have shown that the REM sleep generator is located in the pons and medulla [54–56]. Although discrete lesions of the SLD in rats resulted in an RBD-like phenotype, REM sleep time and transition patterns were not altered [16]. However, lesions extending into the caudal part of the LDT lying dorsal to the SLD reduced daily REM sleep amounts by 50%, with severe fragmentation of not only REM but also of other sleep–wake states [16]. Similar REM reduction and sleep–wake fragmentation were observed in mice following selective and focal elimination of glutamate neurotransmission from this region in mice, as well as by large PPT–LDT–SLD lesions in cats [14,57]. These results suggest that the glutamatergic neurons in the SLD–cLDT region regulate REM sleep amount and transitions while separate populations of reticulospinal neurons in the SLD regulate atonia. As mentioned GABA receptors are involved in the regulation of the SLD. The neurons that release GABA in the SLD are located in the vIPAG and LPT, and they inhibit the REM-on neurons and suppress REM sleep. For example, lesions of the vIPAG–LPT area doubled the amount of REM sleep in rats [16], and inhibition of this region by injections of the GABA agonist muscimol increased REM sleep in cats [58].

Because the vIPAG–LPT and cLDT–SLD contain GABAergic neurons that project to each other, we have proposed that GABAergic neurons in these two regions form a “flip-flop” switch that controls REM sleep [16,25]. The GABAergic neurons in the vIPAG–LPT also inhibit the cLDT–SLD glutamatergic output neurons that directly control corticohippocampal activation and atonia [14,16] (Fig. 1A). Since this model was first proposed, several lines of evidence have supported this formulation. First, microinjections of a serotonin receptor 1A agonist into the PPT region significantly increased REM sleep time and episode number [59]. Because serotonin A1 receptors are seen in GABAergic neurons but not PPT–LDT cholinergic neurons [60], 5-hydroxytryptamine may in fact inhibit REM-off GABAergic neurons as predicted, thereby activating REM-on neurons and producing an increase in REM sleep. Second, Sapin et al. [61] defined a much smaller region in the vIPAG where muscimol injections trigger REM sleep, indicating an important GABAergic input to this region. Third, vIPAG lesions by orexinsaporin increase REM sleep in both orexin knockout and wild type mice [62]. Fourth, vIPAG lesions also are found to increase REM sleep in guinea pigs [63]. Finally, pharmacogenetic activation of the GABAergic neurons in the vIPAG–LPT significantly reduced REM sleep (unpublished data) indicating that the GABAergic neurons in the vIPAG–LPT mediate REM sleep suppression.

We recently eliminated GABAergic transmission from vIPAG/LPT neurons by conditional knockout of vesicular GABA transporter in this region. To our surprise, REM sleep was not altered [14]. Given the strong evidence of GABAergic neurons in the vIPAG/LPT suppressing REM sleep, it is possible that GABA neurons co-contain other inhibitory neurotransmitters whose co-release may be critical for REM suppression. Alternatively these neurons may contain an unidentified vesicular GABA transporter. The vIPAG–LPT region receives multiple inputs from the medial prefrontal cortex, the preoptic sleep active neurons, lateral hypothalamic orexin neurons, GABAergic and melanin-concentrating hormone neurons, and the central amygdala nucleus [3,16,64–68]; these regions thus may modulate REM sleep [3,4]. Besides GABA and glutamate, the monoamine and acetylcholine inputs previously proposed to play a central role in REM control may modulate REM sleep by acting on either one or both REM-on and the REM-off neurons [17,69,70] (Fig. 1A). We have shown that the cLDT–SLD glutamatergic neurons may play a critical role in cortical activation during REM sleep via its projections to the PB and PC [14,71].

Despite extensive lesions in the dorsal pons, REM sleep in cats and rats is reduced by 50% at most. REM sleep was eliminated by electrical but not ibotenic acid lesions of the gigantocellular tegmental field in the rostral ventral medulla [16,72,73]. Transections at this level also eliminated REM sleep and blocked REM sleep and PGO induction by carbachol injection in the perilocus coeruleus in cats [32,74]. This kind of transection may partially be mimicked in patients with locked-in syndrome who may have no REM sleep [75,76]. Thus the medulla may contain REM sleep control neurons, and its interaction with the SLD-cLDT is necessary for REM sleep induction [74]. Boissard et al. [25] have mapped medullary GABAergic and non-GABAergic afferent neurons to the SLD, which were widely distributed in the medial part of the medulla [25]. Partial lesions of this region caused significant reductions in REM sleep that were primarily due to reduction in the number of REM bouts [27]. These results further support the notion that the medulla and pons work together in regulating REM sleep.

5. Neural basis of RBD

Stroke or inflammatory lesion in the dorsal pontine tegmentum causes RBD [77,78], which is well in line with SLD lesions producing RBD-like phenotype in animals. iRBD is an early sign of several neurodegenerative diseases, notably PD, DLB, and MSA, and it has been proposed that neuronal loss in the SLD causes RBD [15]. So far the pathology of the SLD-SC has not been confirmed in iRBD. On the other hand, cell loss in the LC and SC regions has been identified in PD [79,80]; however, whether or not these particular PD patients also had RBD is not known. The close temporal association of RBD preceding synucleinopathies (PD, DLB, and MSA) by a decade or more [81] suggests that SLD-SC pathology may be one major causal factor for the RBD. The neuronal loss in some PD and MSA patients may first start in the medulla and caudal pons including the SLD-SC, as proposed by Braak et al. [79], and then slowly progresses into other rostral areas such as the dopaminergic neurons of the substantia nigra pars compacta (SNc); this occurrence often results in parkinsonism.

In addition to the SLD, there are 3 other potential sites where damage may cause RBD, including the ventral medulla, the ventral pons, and the spinal cord. Because ventral medulla lesions are expected to have much more severe consequences for sympathetic cardiovascular and respiratory functions and because earlier iRBD often is not associated with severe cardiovascular disorders, medulla lesions may be involved in those RBD cases with cardiovascular changes and a lack of complex behaviors [82,83].

If dysfunction of the spinal cord inhibitory interneurons causes iRBD, one also would expect to see myoclonus even during non-REM sleep and wake, a phenotype that has not been reported in iRBD. Finally, Lai et al. [33] reported that lesions of the ventral pontine region that were close to the SNc resulted in periodic leg twitching during REM sleep but not complex behaviors [33]. Because SNc dopaminergic cell lesions do not result in EMG changes in REM sleep, it is considered that nondopaminergic neurons may be involved in muscle tone control during REM sleep. Thus, these observations collectively suggest that iRBD of complex behaviors may primarily be due to the pathology of the SLD/subcoeruleus, and some iRBD cases of simple behaviors may be due to pathology of the multiple sites, including the ventral medulla, ventral pons, and spinal cord. Because REM sleep time and transition generally is normal in iRBD [84], iRBD pathology in the dorsal pons may mostly be confined in the SLD-SC but not the region dorsal to the SLD-SC [16]. Conversely as RBD patients with MSA display REM sleep reductions in addition to RBD [85], we predict that the underlying pathology in these patients includes both cLDT and SLD lesions. Not all PD patients display RBD symptoms and history, which eliminates involvement of SNc dopaminergic neurons in REM sleep regulation and RBD. Lack of muscle tone changes during REM sleep following lesions of the SNc and SN pars reticulata

[86] or in SN pars reticulata alone [87] in rats supports the evidence that the SNc is not significantly involved in atonia regulation during REM sleep (unpublished data). Finally, in sharp contrast to disinhibition of motor activity during REM sleep in RBD, the phasic regulation of some muscles appear to be intact in iRBD; phasic eye movements are not altered [88] and REM sleep penile tumescence appears normal [89]. Thus the circuitry involved in regulating these REM sleep events possibly is not affected in RBD, and these observations support the hypothesis that the SLD may not be involved in these processes.

One perplexing feature of PD with RBD is that parkinsonism is reduced in REM sleep [13]. One possible interpretation is that supplementary and motor cortices and basal ganglia may have different patterns of activity in REM sleep than during wake [90], and dopamine may play a more limited role in the basal ganglia and motor function during REM sleep. Clonazepam, which often is successful in treating RBD [91], may inhibit motor cortex to reduce motor behavior, similar to how clonazepam also reduces epileptic myoclonus induced by cortical dysfunction [92]. Identifying the exact mechanisms by which clonazepam affects cortical activity and RBD may help elucidate not only REM sleep atonia circuitry but also the motor pathways underlying waking behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Putative neural circuitry of rapid eye movement (REM) sleep and REM sleep behavior disorder (RBD). The REM sleep switch consists of reciprocally connected REM-off and REM-on neurons. Although the glutamatergic neurons in the caudal part of the laterodorsal tegmental nucleus and sublaterodorsal nucleus (cLDT-SLD) primarily are involved in generation of REM sleep, GABAergic neurons may aid in transitions into and out of REM sleep. GABAergic neurons in the ventrolateral periaqueductal gray matter/lateral pontine tegmentum (vLPAG-LPT) act to suppress REM sleep by acting on the cLDT-SLD glutamate/GABAergic neurons. Furthermore, these REM-off neurons are under excitatory influences from the medial prefrontal cortex (mPFC), orexin neurons, locus coeruleus (LC),

and dorsal raphe nucleus (DRN), in addition to inhibitory influences from the extended ventrolateral preoptic nucleus (VLPO), the pedunculopontine tegmental nucleus/laterodorsal tegmental nucleus (PPT/LDT) cholinergic neurons, the central amygdala nucleus (CeA), the hypothalamic melanin-concentrating hormone (MCH), and GABAergic neurons. The glutamatergic REM-on neurons in the cLDT-SLD project to the parabrachial nucleus (PB), the precoeruleus nucleus (PC), and the PPT/LDT cholinergic neurons which then activate the forebrain. Glutamatergic neurons in the SLD cause muscle atonia during REM sleep by their activation of the reticulospinal neurons in the VMM and inhibitory interneurons in the spinal cord, which inhibit spinal cord motor neurons (A). In the phasic REM sleep circuit, the phasic (P) active glutamatergic REM-on neurons in the cDLT-SLD, via PB–PC–LDT–PPT, activate the sites in the forebrain and medulla and cortex that regulate phasic REM sleep. For instance, Mo5 phasic regulation is by the neural circuit of the PB–PC to the basal forebrain to the motor cortex to the rostral parvocellular reticular formation (rPCRt) to Mo5. For autonomic control, the circuit consists of PB projecting to the paraventricular hypothalamic nucleus (PVH) to the intermediolateral column (IML) preganglionic neurons (B). The neural pathway is underlying the RBD. Cell loss in the SLD would result in reduction of antagonized control over cortex-driven complex behaviors of spinal cord motor neurons, resulting in RBD. Simple behaviors can be driven by the cortex or the brainstem or spinal cord.