

Effects of Pontine Lesions on REM Sleep

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Abstract Over the past several decades, the neural mechanisms underlying REM sleep have become increasingly understood. A more detailed understanding of the respective roles of the pontine nuclei in the generation of REM sleep and its related phenomenon has allowed for the recognition of specific effects that brainstem lesions have on sleep. In humans, however, the effects of such lesions are limited to case reports and small case series. This article offers a comprehensive review of the basic neurobiology of REM sleep. In addition, we discuss specific clinical effects that various pontine lesions have with regard to REM sleep and the spectrum of clinical sleep disorders characterized by abnormalities in REM-related phenomena. We review the existing literature detailing the interactions between clinical sleep manifestations and brainstem pathology.

Keywords Rapid eye movement sleep · REM atonia · Brainstem lesions · REM sleep behavior disorder · alpha-synucleinopathies · Parkinson's disease · Multiple systems atrophy · Dementia with Lewy body · Narcolepsy

Introduction

Despite the fact that we spend approximately one-third of our lives sleeping, the exact function of sleep remains speculative. The subject of rapid eye movement (REM) sleep, or “paradoxical sleep,” has intrigued philosophers and clinicians throughout history. The leading theories suggest that REM sleep may have its primary purpose in memory consolidation

[1]. Despite this longstanding interest in REM sleep, it has only been within the past one-half of this century that our understanding of the basic mechanisms that drive REM sleep been advanced. In the 1930s, several important studies established the location of the ascending arousal systems in the rostral pons and caudal midbrain. Subsequent work showed that these pathways originate from neurons in discrete cell groups and are associated with specific neurotransmitters. Aserinsky and Kleitman are credited with first discovering REM sleep in 1953 [2]. Over the past several decades, the specific mechanisms and critical neuroanatomical structures that generate REM sleep have been elucidated and with that a recognition regarding the influences of brainstem pathology on REM sleep. Despite this knowledge of the anatomic generators of REM sleep, the literature regarding the effect of brainstem lesions on REM sleep is scarce and consists mainly of case reports and small case series. This review will first focus on the neurobiology of REM sleep with discussion of the specific neural mechanisms of REM sleep. Next, specific REM dysfunctions resulting from brainstem lesions will be discussed with review of the current literature.

Control of REM Sleep

Experimental studies, including animal transection and tissue ablation models, have located the REM generator to a specific collection of neurons in the upper pons. The dorsal aspect of the pons, or pontine tegmentum, contains a network of neurons and ascending fiber tracts collectively known as the reticular formation. Ablation of the more rostral portion of the pontine tegmentum, known as the nucleus reticularis pontis oralis (NRPO), has been experimentally shown to eliminate REM sleep [3]. Within the lateral portion of the NRPO, just ventral to the locus coeruleus (LC), the most critical region for REM sleep is found. This is the

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subcoeruleus area, or sublateral dorsal area (SLD). Neurons within this subcoeruleus region have a high rate of firing only during REM sleep and are referred to as REM sleep-on cells.

Other brainstem structures regulate REM sleep through input to these REM sleep-on cells. These sublateralodorsal, REM sleep-on cells, are normally under gaba-ergic inhibition from nearby interneurons in the ventrolateral periaqueductal gray matter (vlPAG) and adjacent part of the lateral pontine tegmentum (LPT). Firing of these interneurons prevents REM sleep from occurring and are, therefore, called REM sleep-off cells. The onset and termination of periods of REM sleep can be conceptualized by the engineering concept of a flip-flop switch with poles consisting of REM sleep-on cells in the subcoeruleus region and REM sleep-off cells in the PAG and LPT. These cell groups mutually inhibit each other (Fig. 1). Gaba-ergic neurons in the extended ventrolateral pre-optic nucleus (eVLPO), the primary generator of NREM sleep, project to and inhibit the REM sleep-off cells that, in turn, disinhibit the REM sleep-on cells allowing REM sleep to occur. Periods of REM sleep terminate when excitatory input from the posterolateral hypothalamic hypocretin neurons, the noradrenergic locus coeruleus, and the serotonergic raphe nuclei activate the REM sleep-off cells, restoring the baseline inhibition of the REM sleep-on cells. In addition, cholinergic neurons from the pedunculopontine (PPN) and laterodorsal tegmental (LDT) nuclei are active during REM sleep while monoaminergic systems (ie, locus coeruleus) that mediate wakefulness cease firing.

Although the above mechanisms describe the generation of, and transitions into, REM sleep, it is important to also understand the physiology of other REM-related phenomena, such as atonia. REM sleep can be conceptualized as a state of internal arousal, sharing features of both NREM sleep and wakefulness. REM sleep generally comprises about 20 % of total sleep time in adults. The characteristics of REM sleep can be broken down into tonic (persistent throughout the REM period) and phasic (occurring intermittently) features. The major tonic features include electroencephalogram (EEG) desynchronization which resembles the EEG of wakefulness when the eyes are open and consists of a low-amplitude, mixed frequency background rhythm. Additionally, rhythmic theta activity generated by the hippocampus can be seen. Voluntary muscle activity is suppressed, referred to as REM atonia, though the extra ocular muscles, diaphragmatic activity, and inner ear muscles are spared. Some have speculated, from an evolutionary standpoint, that the purpose of REM sleep and the sparing of such functions was to periodically stimulate the brain to allow for a quick transition to wakefulness in the event of a predator attack [4].

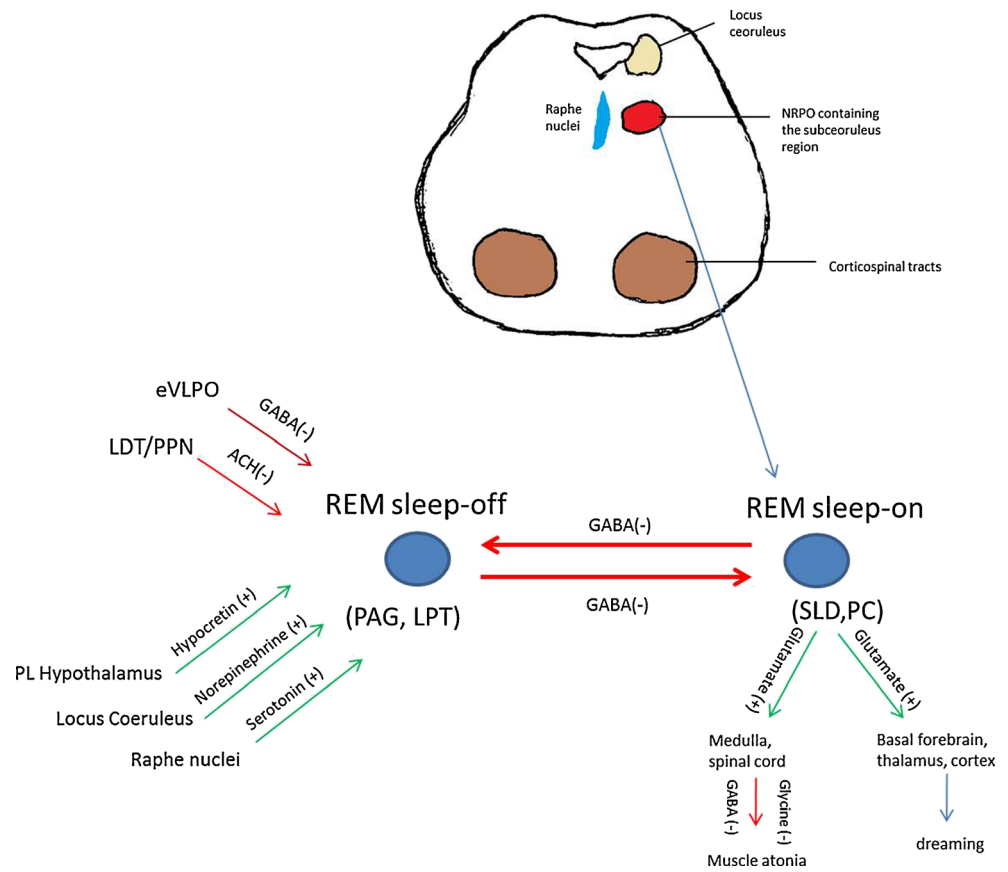
REM atonia serves a vital function of preventing individuals from physically acting out the content of their dreams. Much of the current knowledge regarding REM atonia stems from animal models, and to a lesser extent human studies. The

critical areas responsible for muscle atonia are most likely the PPN and the nucleus magnocellularis of the medial medulla (medullary magnocellular reticular formation, or MMRF) (Fig. 2). Once the REM sleep-on cells in the subcoeruleus region are activated, axons arising from the dorsolateral PPN travel via the tegmentoreticular tract to synapse on cell bodies in the MMRF. The neurotransmitters include excitatory glutamate and acetylcholine. Axons containing glycine and GABA arise from the MMRF, travel in the ventrolateral reticulospinal tract and terminate on interneurons of the spinal cord anterior horn cells. This ultimately results in postsynaptic inhibition and muscle atonia. REM atonia without other REM phenomena can be produced experimentally by injection of cholinergic agonists into the dorsal pons or by electrical stimulation as well as injection of glutamate into the medial medulla [3]. In contrast, loss of REM atonia can be experimentally produced by lesions of the dorsal pons, presumably via interruption of the axons in the tegmentoreticular tract. This is essentially the experimental model for REM sleep behavior disorder in adults.

Additional tonic REM phenomena include penile erections in men, clitoral engorgement in women, and impairment of thermal regulation. The most characteristic REM phenomenon that an individual experiences is dreaming. In fact, subjects awakened during REM sleep will report dreaming in about 85 % of awakenings whereas dreams are rarely recalled after a period of REM sleep has ended [3].

REM sleep derives its name from its major phasic feature, the rapid eye movements. They have a characteristic appearance on the eye leads of a polysomnogram (PSG). These are generally conjugate, irregular, predominantly horizontal or oblique, and sharply peaked eye movements that occur in clusters during a period of REM sleep. Other phasic features include motor, autonomic, and EEG phenomenon. Short brief bursts of transient and irregular muscle activity, often referred to as phasic muscle twitches, may be seen. Irregular respirations and heart rate (sympathetic bursts) occur as a phasic phenomenon. Sawtooth waves on the EEG are trains of triangular, 2–6 Hz frequency waves most notable over the central leads and often precede rapid eye movements. Though not seen on routine EEG, intermittent ponto-geniculo-occipital (PGO) waves, have been recorded prior to and during REM sleep in animals with electrodes placed in the pontine tegmentum, lateral geniculate body of the thalamus, and the occipital cortex. These PGO waves seem to be integral to the development of REM sleep though the exact details are poorly understood. They appear to serve as the physiologic correlate of the neural pathways mediating REM phenomenon rostral to the pons [3]. PGOs are large amplitude, isolated potentials, appearing 30 or more seconds before the onset of REM sleep. Once in REM sleep PGOs occur in bursts of 3–10 waves preceding the rapid eye movements. They likely have a role in the production of dream imagery.

Fig. 1 Control of REM sleep. This diagram illustrates the control of REM sleep via a flip-flop switch model including regulatory influences on these cells. Input from the eVLPO and PPN results in inhibition of the REM sleep-off cell which, in turn, disinhibits the REM sleep-on cells allowing REM sleep to occur. Hypocretin, Norepinephrine, and Serotonin from their respective nuclei result in activation of REM sleep-off cells thereby restoring the baseline inhibition of the REM sleep on cells and terminates REM sleep. *ACH* Acetylcholine, *eVLPO* extended ventrolateral preoptic nucleus, *LDT* laterodorsal tegmentum, *LPT* lateral pontine tegmentum, *NRPO* nucleus reticularis pontis oralis, *PAG* periaqueductal gray, *PC* procoeruleus region, *PPN* pedunculopontine nucleus, *SLD* sublater dorsal area



Brainstem Lesions Effect on REM Sleep

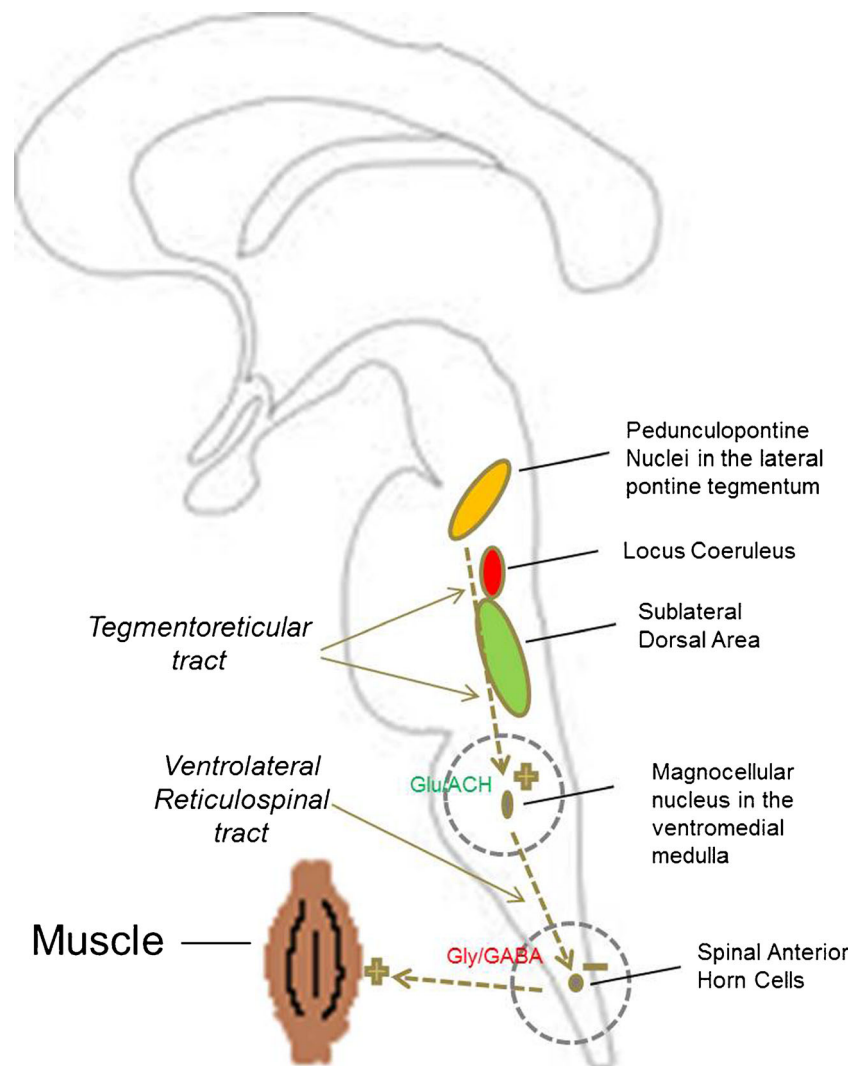
As one might expect based on an understanding of the above physiology, lesions in the brainstem can have profound effects on sleep with alteration of the typical feature of REM sleep. The literature of humans with brainstem abnormalities and disrupted REM sleep as documented by polysomnographic recordings is relatively scarce and consists only of a limited number of case series and case reports. Brainstem lesions involving critical pontine structures can essentially be categorized into 2 main patterns of REM disruption: (1) alteration of sleep architecture with reduction or absence of REM sleep, and (2) REM sleep behavior disorder (RBD). The role of pontine lesions in the generation of narcolepsy is less well established but will also be discussed.

Reduction of Total REM Sleep Caused by Brainstem Lesions

In 1971, Feldman reported the first case of a brainstem lesion and a sleep abnormality [5, 6]. A 36-year-old woman with vertebral artery trauma from a motor vehicle accident and chronic locked-in syndrome was noted to have only 3 %–4 % REM sleep. Wilkus et al reported no REM sleep during a 5-hour nocturnal EEG on a comatose patient with an extensive

pontine infarct [7]. A few years later several case reports demonstrated contradictory findings [8–10] casting doubt on the relation between brainstem lesions and REM sleep abnormalities. In 1976, Markand and Dyken carried out more sophisticated polygraphic recordings on 7 patients with locked-in syndrome due to a vascular etiology [11]. Of the 7, 3 had absent REM sleep, 2 had decreased REM sleep, and 1 had no sleep at all. They concluded that bilateral extensive lesions in the midpontine region are likely to be associated with severe sleep abnormalities to include absence or reduction of REM sleep. These earlier case studies were limited by the lack of CT or MRI findings to confirm localization. In 1984, Lavie reported a patient with nearly total absence of REM sleep as a result of a shrapnel injury affecting the pons as shown on a CT [12]. In 1988, Autret et al reported sleep abnormalities in 4 cases with medial pontine tegmentum lesions documented by CT [13]. Two of these patients had complete absence of REM sleep whereas the other 2 demonstrated a decreased REM percentage. These early reports helped to provide further confirmation of the role of pontine structures in the generation of REM sleep in humans that had been previously established by pharmacologic and lesional studies in animals, mainly cats.

Fig. 2 The neural pathways mediating REM atonia. Axons arising from the dorsolateral pedunculopontine nucleus travel via the tegmentoreticular tract to synapse on cell bodies in the nucleus magnocellularis of the ventromedial medulla. The neurotransmitters released onto these cell bodies in the nucleus magnocellularis include excitatory glutamate and acetylcholine. Axons from these nuclei then travel in the ventrolateral reticulospinal tract and terminate on interneurons of the spinal cord anterior horn cells. Release of glycine or GABA at these anterior horn cell interneurons ultimately results in postsynaptic inhibition and muscle atonia



With continued improvement in imaging capabilities, further case reports and case studies have demonstrated the breadth of pathologies that can affect these structures and, in turn, affect REM sleep. In 2000, Kimura et al reported a patient with a left upper pontine stroke who had both a reduction of REM sleep as well as REM sleep behavior disorder [14]. Valldeoriola et al reported a case of suspected primary CNS lymphoma in an HIV positive patient affecting the pons resulting in absence of REM sleep as well as bilateral horizontal gaze palsy as the sole neurologic abnormalities [15]. This report illustrated the anatomic relation between REM generators and those areas associated with horizontal eye movements. In this report, citing some of the earlier studies, they also postulated that bilateral damage to the pontine tegmentum is necessary for abolition of REM sleep. In 2005, Landau et al prospectively reported out the PSG findings in 8 consecutive patients with brainstem lesions confirmed on MRI, 6 of which had

intrinsic pontine lesions [6]. Three of these patients had cavernous hemangiomas whereas the other 3 had strokes. Four of these patients with lesions affecting some portion of the posterior pons, the expected locations of the subcoeruleus area, had decreased REM sleep percentage with respect to age matched controls. Note that all 4 of these patients had unilateral lesions in contrast to the postulation by Valldeoriola et al. Kagitani-Shimono also reported a case of absent REM sleep related to a pontine cavernous hemangioma [16]. REM sleep reduction has also been reported in olivopontocerebellar degeneration [17]. Loos et al reported a child with reduced REM sleep secondary to a brainstem meningioma [18]. In summary, knowledge of the neurobiology of REM sleep in conjunction with these numerous case studies clearly suggest that lesions involving critical REM generating structures in the pons can result in reduction, or even total absence of REM sleep.

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by intermittent loss of the normal skeletal muscle atonia during REM sleep. Clinical manifestations include excessive, often elaborate and violent motor activities associated with dreaming. The specific motor activities are variable and range from simple limb movements to complex motor behaviors such as calling out or thrashing around as if to fight off attackers during sleep. The potential for harm to self or bed partner can be quite significant. Significant injury results from falls out of bed, walking into walls or furniture, or even falling downstairs or out of a window. The diagnosis is usually suspected clinically, however, confirmatory PSG is considered obligatory per the most recent International Classification of Sleep Disorders (ICSD-3) [19]. According to the ICSD-3, diagnostic criteria for RBD includes the following: (1) repeated episodes of sleep related vocalization and/or complex motor behaviors, (2) the behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep, (3) polysomnographic recording demonstrates REM sleep without atonia (RWA), and (4) the disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use. Therefore, the PSG offers confirmatory findings in the form of excessive motor activity during REM sleep (RWA) as well as visual confirmation of the complex behaviors emanating from REM sleep. Furthermore, a PSG also excludes the possibility of an underlying sleep related breathing disorder (“pseudo-RBD”) for which effective treatment may eliminate the dream enactment behaviors.

RBD is usually a chronic disorder that occurs more often in men, typically after the age of 50. The exact prevalence is not known with much certainty; however, a prevalence of 0.38 %–0.5 % is reported in the elderly and the general population [20, 21•]. RBD can be idiopathic or secondary, associated with an underlying neurodegenerative synucleinopathy such as Parkinson’s disease, Dementia with Lewy Body or Multiple Systems atrophy [19]. Other secondary etiologies include medications, particularly antidepressants, alcohol and drug abuse, or withdrawal and caffeine. Less appreciated secondary etiologies include focal brainstem lesions of various pathologies. In children and young adults, RBD is rarely idiopathic and usually associated with secondary etiologies such as narcolepsy, brainstem tumors, antidepressant medications, neurodevelopmental disorders and various rare conditions [19]. Frauscher et al suggested that idiopathic RBD is actually uncommon and more likely to be secondary to an underlying neurodegenerative disorder, medication or brainstem lesion [22•].

Various etiologies have been reported in association with RBD. These include pontine infarcts [14, 23–27], pontine tumors [27–29], demyelinating lesions in the dorsal pontine

tegmentum [26, 30–32], pontine inflammatory lesions [26, 33–35], and vascular malformations of the pontomesencephalic tegmentum [26, 36] (Table 1). As alluded to previously, experimental lesions to the sublateralodorsal area in cats [37] can reproduce REM sleep without atonia accompanied by dream enactment behaviors. These case reports support this animal research, and provide compelling evidence that lesions within or near the mesencephalic and pontine tegmentum are associated with human RBD. Furthermore, although the animal models suggest that bilateral lesions are necessary [38], several of these case reports provide evidence that a unilateral pontine tegmental lesion is sufficient to cause RBD in humans [27, 35]. Based on this evidence, some authors recommend routine brain MRI in the evaluation of older adults with RBD to fully exclude brainstem lesions, especially in those with vascular risk factors [14, 27]. In 1 series of 6 randomly selected patients with RBD, 3 were noted to have lacunar infarcts involving the dorsal pontomesencephalic on MRI [25]. Whether these lesions are causative or incidental is disputable. This is particularly true in patients of advanced age in whom asymptomatic and nonspecific white matter lesions are not an uncommon finding. At minimum, one should strongly consider neuroimaging in RBD when 1 or more of the following are present: (1) acute or subacute presentation, (2) additional neurologic signs or symptoms are present, (3) RBD in young, non-narcoleptic patients, and (4) the RBD is not better explained by another current disorder (ie, Parkinson’s disease, narcolepsy, medication use, etc) [26].

The exact anatomic location of lesions associated with RBD as demonstrated on neuroimaging have been inconsistent [31]. In humans, the specific nuclei, projections, and neurochemical systems involved in RBD pathophysiology are not definitively characterized. In addition to the aforementioned brainstem structures invoked in RBD pathophysiology (pedunculopontine nucleus and nucleus magnocellularis), other mesopontine structures such as the substantia nigra, locus ceruleus, and laterodorsal tegmental nucleus have also been implicated [21•]. There has also been case reports of RBD associated with limbic system damage without primary brainstem impairment [33, 39, 40]. Nevertheless, it seems evident that lesions affecting these pontomedullary pathways which anatomically and functionally mediate REM sleep atonia be regarded as plausible etiologies of RBD.

RBD and Neurodegenerative Disease

There is accumulating evidence to suggest that “idiopathic” RBD actually represents an early manifestation of an evolving neurodegenerative disorder [21•]. RBD is very common in several neurodegenerative diseases involving progressive neuronal loss in the lower brainstem region. Collectively, the synucleinopathies which include Multiple Systems Atrophy

Table 1 A Summary of case reports implicating focal lesions of the brainstem with REM sleep behavior disorder

Authors	Type of lesion	Location of lesion
Kimura et al [14]	Ischemic infarct	Left upper pons
Plazzi et al. [52]	Multiple sclerosis	Pons
Provini et al [36]	Cavernoma	Pontomesencephalic tegmentum
Zambellis et al [28]	Neurinoma	Left pontocerebellar angle
Tippman-Peikert et al. [31]	Multiple sclerosis	Dorsal pons
Condurso et al. [24]	Ischemic infarct	Dorsomedial pons
Mathis et al. [34]	Encephalitis	Dorsomedial pontine tegmentum
Xi et al. [27]	Ischemic infarct	Right paramedian pons
Gomez-Choco et al. [32]	Multiple sclerosis	Pons
Limousin et al. [35]	Inflammatory of undetermined etiology	Right pontine tegmentum
Culebras et al. [25]	Ischemia	Pons
Compta et al. [33]	Ma-2 encephalitis	Dorsolateral midbrain
Jianhua et al. [29]	Lymphoma	Pons

(MSA), Parkinson's disease (PD) and Dementia with Lewy Body (DLB), have a strong association with RBD and are characterized by abnormal insoluble aggregates of alpha-synuclein protein in specific brainstem nuclei. RBD is present in over 90 % MSA patients, approximately 50 % of DLB patients, and up to 46 % of PD patients [19]. Multiple studies involving idiopathic RBD patients followed prospectively have demonstrated eventual development of a neurodegenerative synucleinopathy [19, 41]. Two recently reported series reported as high as 81 % and 82 % eventual conversion rates within 20 years from idiopathic RBD to parkinsonism/dementia [19]. In a seminal paper by Schenck et al RBD preceded the first manifestation of a neurodegenerative disorder with a mean latency of 12.7 years [41]. Only infrequently does RBD occur in the tauopathies (such as Alzheimer's disease) and other neurodegenerative diseases [21•]. This tendency suggests a selective vulnerability of key brainstem neural networks shared uniquely by the synucleinopathies and RBD and provides further insight into human RBD pathophysiology.

Braak et al proposed a neuropathologic staging system for PD. The observations of clinical and pathologic progression are applicable to the onset and evolution of RBD in PD [21•, 42, 43]. In this staging system, PD pathology starts with the premotor and preclinical stages 1 and 2 that remain confined to the medulla and olfactory bulb. This is followed by the inclusion of the substantia nigra and other nuclear grays of the midbrain and basal forebrain in stages 3 and 4, before involvement of the cortical structures in the final stages (stages 5 and 6). Essentially, this staging system posits a temporal sequence of alpha-synuclein pathology in the brain beginning mainly in the medulla and olfactory bulb with subsequent progression to more rostral structures. RBD occurs when prominent degeneration in the sublateral dorsal region occurs. This temporal sequence of pathology could explain why RBD precedes

parkinsonism and cognitive decline (stages 3 and 4) and dementia (final stage) in many patients with Lewy-body pathology. Further supporting this evolution are studies demonstrating other early markers of a neurodegenerative synucleinopathy in patients with "idiopathic RBD". These include olfactory dysfunction, subtle motor signs, subtle characteristic neuropsychological abnormalities (involving attention/executive and visuospatial domains), more widespread electroencephalographic slowing and various neuroimaging abnormalities (PET, SPECT, MR spectroscopy) [21•].

Narcolepsy and Brainstem Lesions

Narcolepsy is also characterized by abnormal expressions of REM sleep. RBD is often strongly linked with narcolepsy and RBD associated with narcolepsy is now considered a distinct phenotype [19]. RBD is present in 7%–36 % of patients with narcolepsy [44]. Narcolepsy is most commonly considered a sporadic disorder with a genetic susceptibility, associated with a deficiency of hypocretin in the hypothalamus. Hypocretin is a neuropeptide that promotes wakefulness and inhibits REM sleep. Impairment of this hypocretin system results in the classic symptomatology of narcolepsy: excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis. More recent evidence strongly suggests that this hypocretin deficiency results from an autoimmune attack of the hypocretin producing neurons in the posterolateral hypothalamus [45].

Though typically sporadic, symptomatic, or secondary etiologies of narcolepsy, usually due to structural lesions involving the hypothalamus, have been reported [33, 34, 46–51]. Symptomatic cases related to brainstem lesions have also been described though this relationship is far less well established [33, 34, 46, 52–57]. Based upon the above discussion regarding the anatomy of REM sleep and related muscle atonia, an

isolated pontine tegmental lesion may easily explain RBD and cataplexy. In addition, the dorsomedial pontine tegmentum contains the PPN and LDT which are the main cholinergic neurons of the ascending arousal system. Axonal fibers from the locus coeruleus project to the hypocretin-containing neurons in the hypothalamus. Considering this relation with key structures involved in maintaining wakefulness, lesions of the pons could explain the hypersomnolence component. Therefore, a focal pontine lesion could potentially result in the cardinal manifestations of narcolepsy. Many of the reported symptomatic cases, whether involving lesions of the hypothalamus or brainstem, were HLA-DR2 positive suggesting a genetic susceptibility. This has led some investigators to postulate that certain anatomic lesions might induce, facilitate, or accelerate a narcoleptic syndrome only in genetically predisposed people [34, 47, 49, 52].

Conclusions

Although some of the specific details regarding the physiology of human REM sleep are still being determined, many of the basic mechanisms have been described. Pontine nuclei, particularly the REM sleep-on cells in the sublateral dorsal area as well as the REM sleep-off cells in the ventrolateral peri-aqueductal gray and the lateral pontine tegmentum, play critical roles in regulating REM sleep and its various features. Brainstem lesions affecting these areas in the pons can have profound effects on REM sleep physiology. In reviewing the existing literature, it is evident that pontine lesions, regardless of etiology, can affect REM sleep by way of diminishing or eliminating the total amount of REM sleep. In addition, a pontine lesion can be a secondary etiology of RBD. Though narcolepsy is generally thought of as a disorder related to hypothalamic dysfunction, there is growing evidence that the aforementioned brainstem areas may also play a role and may represent another localization in the less common symptomatic forms. A sound understanding of the neurobiology of REM sleep as well as the clinical manifestations of lesions affecting the involved brainstem structures is necessary for any provider who manages these disorders.

Compliance with Ethics Guidelines The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

Conflict of Interest Mark E. Landau, and Craig Carroll declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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