

Physiological and Anatomical Link Between Parkinson-Like Disease and REM Sleep Behavior Disorder

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease that is caused by a loss of neurons in the ventral midbrain. Parkinsonian patients often experience insomnia, parasomnias, and daytime somnolence. REM sleep behavior disorder (RBD) is characterized by vigorous movements during REM sleep, and may also be caused by neuronal degeneration in the central nervous system (CNS); however, the site of degeneration remains unclear. Both Parkinsonism and RBD become more prevalent with aging, with onset usually occurring in the sixties. Recent findings show that many individuals with RBD eventually develop Parkinsonism. Conversely, it is also true that certain patients diagnosed with Parkinsonism subsequently develop RBD. Postmortem examination reveals that Lewy bodies, Lewy neurites, and *α*-synuclein are found in brainstem nuclei in both Parkinsonism and RBD patients. In this article, we will discuss evidence that Parkinsonism and RBD are physiologically and anatomically linked, based on our animal experiments and other studies on human patients.

Index Entries: REM sleep behavior disorder; substantia nigra; ventral tegmental area; retrorubral nucleus; locus coeruleus; nucleus magnocellularis; Lewy bodies; Lewy neurites; *α*-synuclein.

Introduction

It is well-established that a slow, progressive loss of dopaminergic neurons in the substantia nigra (SN) and ventral tegmental area (VTA)

(1) resulting from a decrease in the density of dopamine transporter molecules (2-4) in the basal ganglia causes Parkinsonism. Yet the observed changes in density of dopamine receptors in the striatum in Parkinson's Disease (PD) are inconsistent, with an increase (5,6) or no change (7,8) compared with age-matched controls reported. REM sleep behavior disorder (RBD) is a motor disorder that

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occurs during sleep (9,10). As in Parkinsonism, a decrease in the density of the presynaptic dopamine transporter (11) and dopamine terminals (12) with no change in dopamine D2 receptor density (11) in the striatum has also been reported in RBD patients. Many patients have both RBD and Parkinsonism. In this article, we propose that the linkage of these disorders results from the anatomical proximity of their neurological substrates.

Sleep and Sleep-Related Motor Disorders in PD

In addition to motor disability (Table 1), sleep attacks and insomnia are frequently seen in PD patients (13). Insomnia may result from sleep fragmentation, frequent arousal, and difficulty in falling asleep (14). Polygraphic recordings have revealed that an increase in sleep latency, frequent awakening, an increase in light sleep, and a decrease in slow-wave sleep (SWS), stages 3 and 4, are common in PD-like patients (15,16; Table 1). REM sleep is either reduced or unchanged in Parkinsonism (17; Table 1). The poor quality of nocturnal sleep is the most likely cause of daytime sleepiness. Several factors, including aging (18,19), medication (20), and motor disabilities, may contribute to the sleep disturbances seen in Parkinsonism. However, polysomnographic recording showed a significant decrease in total sleep time in drug-free PD patients compared with age-matched controls (21). The abnormal sleep organization also worsens with the progression of Parkinsonism (22).

In normal individuals, muscle activity is reduced during SWS, and atonia occurs during REM sleep. In contrast, high-amplitude tonic muscle activity and phasic muscle twitches in SWS and REM sleep are seen frequently in the PD-like patient (Table 1). Sleep recordings have demonstrated that body movements (23), periodic leg movement (PLM) (21,24), and tremor and phasic muscle activity (25) are seen frequently during SWS in PD-like patients (Table 1). These muscle activities are significant during light sleep and gradually diminish as

sleep progresses from stage 1 to stage 4 (25). In REM sleep, muscle tone is present in PD-like patients (17,26). The frequency of phasic muscle activity in REM sleep seen in Parkinsonism is also higher than in normal persons (25,27).

Sleep and Sleep Disorders in RBD

In contrast to the PD-like patient, an increase (28) or no change (29) in total sleep time is reported in idiopathic RBD patients. Increases in total sleep time result from an increase in SWS stages 3 and 4, REM sleep, or both (Table 1). Eighty-four percent of RBD patients showed an increase in SWS by an average of 25.8% compared with age-matched normal subjects (30). A significant increase in REM sleep has also been reported in 43% of RBD patients, whereas no change in REM sleep time is seen in the remaining 57% of RBD patients (30). However, when RBD accompanies other neurological diseases, such as Shy-Drager syndrome, dementia, and olivopontocerebellar atrophy (31,32), a decrease in total sleep time and stage 4 sleep occurs.

Dream-enacting behaviors, were described by Schenck et al. (10) in their initial description of RBD. These behaviors include laughing, talking, shouting, kicking, jumping out of bed, walking, and running (31,33). REM sleep with the presence of skeletal muscle tone is frequently recorded in RBD patients; however, REM sleep without atonia is not a criterion for RBD (Table 1). REM sleep with atonia or both with and without atonia is typically present in RBD (34,35). REM sleep without atonia may also be observed in patients with olivopontocerebellar degeneration (36,37), cerebellar atrophy, Shy-Drager syndrome, and progressive supranuclear palsy (38). As in PD-like patients, phasic muscle activity during SWS is also increased in RBD patients. Arm and leg twitching, myoclonus, PLMs, and body movement are observed during SWS (29,32). In a study of 96 RBD patients, 61% had PLM and 38% experienced aperiodic limb movement throughout the night in all stages of sleep (28).

Table 1 Sleep and Motor Activity in Human Parkinsonism and RBD and in the Lesioned Cat

	Human patient		Lesioned cat	
	Parkinsonism	RBD	RVMD	VMPJ
Sleep organization				
Total sleep time	decreased	increased	decreased	increased
Light sleep	increased	no change	no change	no change
REM sleep	decreased or no change	increased or no change	decreased or no change	increased or no change
Motor activity				
Waking	rigidity resting tremor akinesia	normal	normal	normal
SWS	t phasic activity	t phasic activity	t phasic activity	t phasic activity
REM sleep	t phasic activity without atonia	t phasic activity with and/or without atonia	t phasic activity with and/or without atonia	t phasic activity with and/or without atonia

Brainstem Neural Abnormalities in PD and RBD

Neuroanatomical studies have revealed that neuronal degeneration is present in several areas of the brainstem in PD-like and RBD patients. In Parkinsonism, neuropathological changes are found in the dopaminergic system in the ventral midbrain, as well as in the noradrenergic, serotonergic, and non-monoaminergic neurons of the brainstem. A study using the immunohistochemical technique found that the number of dopaminergic neurons in the SN and dorsal raphe nucleus (DR), serotonergic neurons in the suprallemniscal area (B9), median raphe (B8), and medullary raphe pallidus (B1)—as well as the substance P-like neurons in the Pedunculopontine nucleus (PPN) and the dorsal motor nucleus of the vagus—is greatly reduced in PD-like patients (39). A significant reduction in the number of catecholaminergic neurons in the parabrachial nucleus (40), locus coeruleus (LC) (41), cholinergic neu-

rons in the PPN and the vagal motor nucleus (42) were also reported in idiopathic PD. Similar findings are also reported for RBD. Post-mortem examination has revealed that the number of dopaminergic neurons in the SN and noradrenergic neurons in the LC are reduced in RBD patients (43).

In 1912, Lewy first reported that cell inclusions were seen in the substantia innominata and the dorsal motor nucleus of the vagus in PD (44). Subsequently, Tretiakoff (45) reported that these cell inclusions were seen in neurons in the substantia nigra. Thus, he named these cell inclusions Lewy bodies. Lewy neurites are elongated inclusions located in the neural processes. Although Lewy bodies and Lewy neurites were first identified in the central nervous system (CNS) of PD, we now know they appear in several other neurodegenerative diseases, diffuse Lewy body disease (46), Alzheimer's disease (AD) (47), and RBD (48). These neuronal abnormalities are found in several brainstem nuclei in both PD-like and RBD patients (Table 1). Hematoxylin & eosin (H & E) stained tissue showed that Lewy bod-

Table 2 Lewy body and Lewy Neurite in the Brainstem in PD and RBDs

	PD	RBD
Dopaminergic Retrorubral nucleus (A8) Substantia nigra (A9)	Lewy body (39) Lewy body (39,49,58,61,65) Lewy neurite (58,59,61) Lewy body (39,49,65) (39)	Lewy body (48,51) Lewy neurite (48,51)
Ventral tegmental area (A10)		
Dorsal raphe nucleus (B6) Noradrenergic		
Locus coeruleus/subcoeruleus (A6)	Lewy body (39,49,58,65)	Lewy body (48,51)
Parabrachial nucleus	Lewy neurite (58) Lewy body (49)	Lewy body (48)
Serotonergic Raphe magnus (B3)	Lewy body (61) Lewy neurite (61)	
Dorsal raphe nucleus (B6) Median raphe (B8) Supralemniscal area (B9) Other systems	Lewy body (39,49,65) Lewy body (39)	Lewy body (48) Lewy body (48)
Pedunculopontine nucleus		
Pontine inhibitory area Nucleus gigantocellularis Nucleus magnocellularis	Lewy body (39,49,65) Lewy body (49) Lewy body (39,60,62) Lewy body (39,60,62) Lewy neurite (60,61)	Lewy body (48) Lewy body (48) Lewy body (48) Lewy body (48)

ies are seen in the SN, VTA, LC, PPN, and B8 group (49,50). Immunohistochemistry combined with the H & E technique demonstrated that Lewy bodies are found in i) dopaminergic neurons in the SN, VTA, and retrorubral nucleus (RRN), and DR, ii) LC noradrenergic neurons, iii) serotonergic neurons in the B8 and B9, and (iv) neurons in the PPN, and medullary gigantocellular (NGC) and magnocellular nuclei (NMC) (39) in PD patients (Table 2). Similarly, Lewy bodies are found in the SN, LC, MR, PPN, NGC, and NMC in RBD patients (48,51); Table 2).

Alpha-synuclein, a presynaptic protein (52), is the major component of neuronal Lewy bodies and Lewy neurites (53), as well as glial-cell inclusions (54). Physiologically, α -synuclein may play an important role in the maintenance and stabilization of fully mature synapses (55). Pathological changes of α -

synuclein result in the loss of its ability to bind to the synaptic vesicle (56). Abnormal aggregation of α -synuclein forms inclusion bodies, which are deposited in Lewy bodies and Lewy neurites (57). Thus, immunohistochemistry of α -synuclein may be more accurate than the H & E stain in the identification of Lewy bodies and Lewy neurites. In Parkinsonism, α -synuclein is found in the SN, LC/subcoeruleus, medullary raphe nuclei, and the ventral part of the NGC that corresponds to the NHC in the cat (58-60; Table 2). Using α -synuclein immunohistochemistry, Lewy neurites have been found in the NMC (61), and glial inclusions are also found in the SN, LC, and dorsal motor vagus nucleus in PD-like patients (54). A very similar pattern of distribution of α -synuclein is also found in RBD (Table 2). Alpha-synuclein is seen in the SN and LC in human RBD patients (51).

Changes in Sleep Organization, Muscle Activity and Neuronal Degeneration in Animal Experiments

The use of an animal model to study progressive neurodegenerative disease offers the advantage of allowing the experimental identification of specific sites, neural circuits, and neurotransmitters that produce the symptoms of the disease. *n*-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxic substance, that mainly destroys dopaminergic neurons, but affects other monoaminergic neurons, LC noradrenergic and raphe serotonergic (62). Systemic application of MPTP induces Parkinsonism in humans and animals (63,64). Lewy bodies are found in the MPTP-treated monkey (65) and baboon (66). However, MPTP-treated animals do not fully express the key symptoms of human Parkinsonism. For example, sleep organization was unaltered after MPTP treatment, despite severe dopaminergic neuron loss in the SN and VTA (67).

A common feature of the pontine or medial medullary lesion in the cat is REM sleep without atonia (68-72). Cats with a lesion in the pontine inhibitory area (PIA) (69,73)—the region in which carbachol injection induces REM sleep-like activity—or medial medulla (72) express orienting, attack, and walking behavior during REM sleep. Motor hyperactivity in REM sleep induced by pontine and medullary lesion in the chronic animal resembles motor activity in REM sleep in human RBD patients. However, neuroanatomical and neurological testing have shown that the PIA is fairly normal in RBD patients (74). Unlike human RBD, sleep organization is not permanently changed after lesions in the PIA or medial medulla in the cat. Cats that received neurotoxic lesions in the PIA (71) or medial medulla showed a decrease in REM sleep without a change in SWS. In contrast, electrolytic lesions of the PIA produced a decrease in both SWS and REM sleep (73). However, the

sleep-wake pattern returned to the baseline level 2-3 wk after lesions in the PIA (71,73) and medial medulla (72).

We first used decerebrate animals to determine the brainstem area and neurotransmitters that participate in the modulation of muscle activity. We found that repetitive electrical stimulation in the ventral mesopontine junction (VMPJ) suppressed muscle tone during stimulation, whereas muscle twitches were elicited between stimulations (75). We theorized that the VMPJ might be involved in the control of muscle activity. Using N-methyl-D-aspartate (NMDA) microinjections, we found that lesions in the VMPJ produced spontaneous or sensory-induced (touching, air jet application) muscle twitches in the decerebrate cat (76). Muscle activity induced by VMPJ lesion appeared as a rhythmic stepping-like movement, a long-duration clonus, or a brief myoclonus. In contrast, muscle activity remained unaltered when the lesion areas were outside of the VMPJ—for example, in the dorsal midbrain and pons as well as in the PIA.

The VMPJ includes the caudal part of the VTA, retrorubral nucleus, ventral mesencephalic reticular formation, and the rostroventral part of the paralemnisal area of the pons (Fig. 1). The VMPJ is a heterogeneous region that contains dopaminergic, GABAergic, glutamatergic, and serotonergic neurons (77-82). Anatomical studies using retrograde transport of WGA-HRP combined with immunohistochemistry showed that glutamatergic and non-glutamatergic neurons in the VMPJ project to the NMC (79; Fig. 1). Based on anatomical findings, we hypothesized that VMPJ modulation of muscle activity could be mediated through the NMC. Electrical stimulation of the NMC could suppress muscle tone (83-85). Application of non-NMDA and corticotropin-releasing factor (CRF) agonists to NMC also suppressed muscle tone (85-87). We tested our hypothesis using the microinjection technique. We found that microinjection of non-NMDA or CRF agonists into the NMC blocked VMPJ lesion-induced muscle hyperactivity (88).

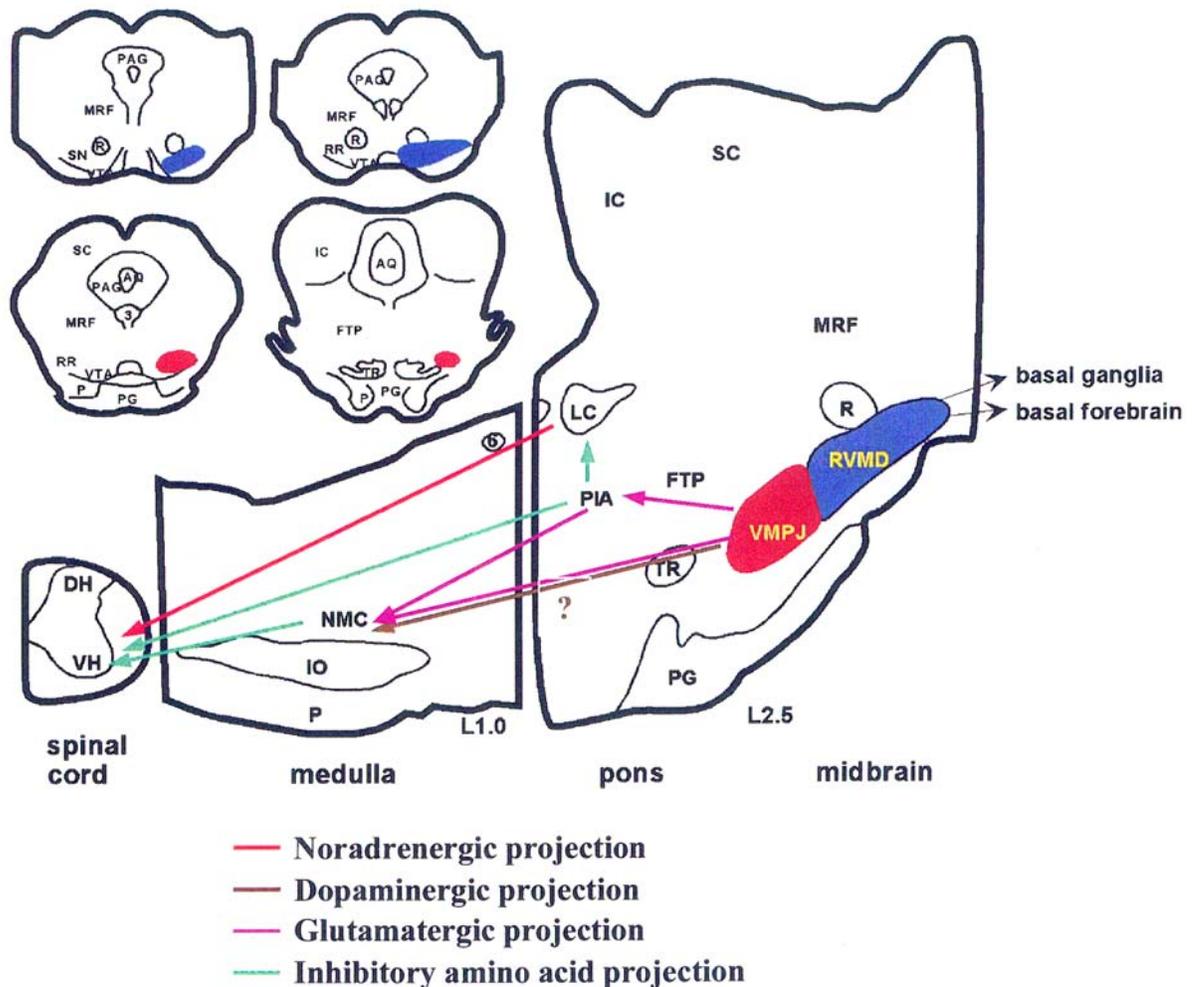


Fig. 1. Shows some of the neural circuitry in the brainstem, which we believe acts to regulate sleep motor activity. The frontal sections on the upper left show areas of the rostral ventral midbrain (RVMD, dark gray area) and ventral mesopontine junction (VMPJ, light gray area). The RVMD includes the ventral mesencephalic reticular formation (MRF), the dopaminergic nuclei of the substantia nigra (SN) pars compacta and reticulata, the rostral part of the ventral tegmental area (VTA), and the retrorubral nucleus (RR). The ventral mesopontine junction (VMPJ) includes the caudal part of the VTA, RR, and MRF, as well as the rostral part of the paralemniscal tegmental field (FTP) of the pons. The sagittal sections shown on the bottom and left sides illustrate projections from the RVMD, VMPJ, pontine inhibitory area (PIA), and nucleus magnocellularis (NMC). Neurons in the RVMD project to the basal ganglia (124) and basal forebrain (125,126). However, the existence of an axonal projection from the VMPJ to the LC remains unclear, as does the transmitter phenotype of this projection and the projection between the VMPJ and NMC. Abbreviations: AQ, aqueduct; DH, dorsal horn; IC, inferior colliculus; IO, inferior olive; LC, locus coeruleus; P, pyramidal tract; PAG, periaqueductal gray; PC, pontine gray; R, red nucleus; SC, superior colliculus; TR, tegmental reticular nucleus; VH, ventral horn; 3, oculomotor nucleus; 6, abducens nucleus.

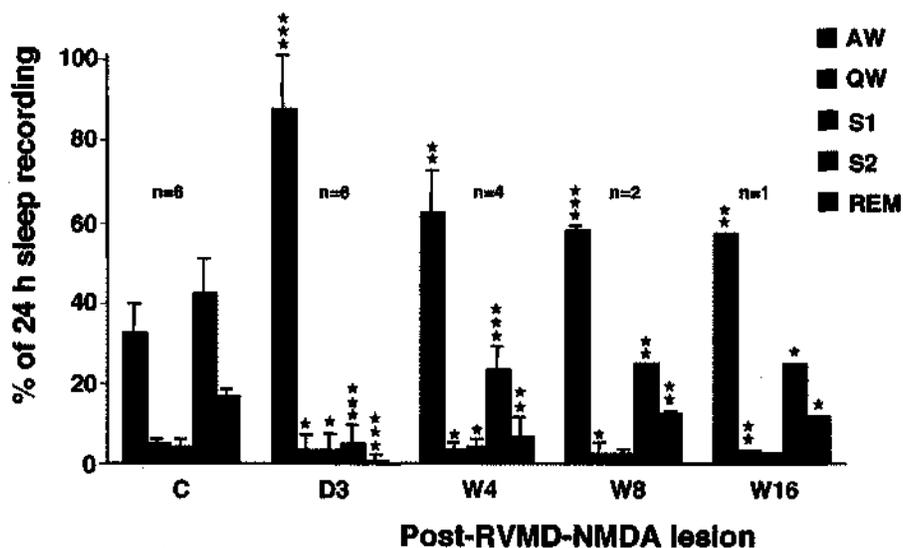


Fig. 2. Percentage of time spent in each state during the 24-h recording period before and after RVMD lesion. A significant change in each sleep-wake state occurred on d 3 post-NMDA-RVMD lesion. All stages of the sleep-wake cycle except S1 remained statistically different from the baseline control value over the entire 4-mo period of the experiment. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. (From: Lai et al. [1999] *Neuroscience* 90, 469-483.)

Based on our finding in the decerebrate cat that lesion of the VMPJ produces motor hyperactivity, we wanted to determine if the same lesion would generate motor abnormalities in the otherwise intact animal. NMDA (0.5 M/0.5 μ l) lesions in the VMPJ produced periodic muscle twitches during SWS, and increased phasic and tonic muscle activity during REM sleep (89; Table 1). Sleep organization was also changed after VMPJ lesion (Table 1). An increase in SWS (5-26%) and REM sleep (20-74%) was observed in the cat after VMPJ lesion (90). The increase in sleep lasted throughout the 4-mo period of observation. The increase in muscle activity during SWS and REM sleep, as well as increased amount of SWS and REM sleep seen in the VMPJ-lesioned animals, resembles the muscle activity during sleep and the increased sleep seen in RBD patients (30).

In contrast to the VMPJ lesion, NMDA lesion in the rostral ventral midbrain (RVMD), which is adjacent to the VMPJ (Fig. 1), produced

insomnia. The RVMD area, which corresponds to the neurodegenerative areas of Parkinsonism, includes the SN, VTA, retrorubral nucleus (RR), and ventral mesencephalic reticular formation. NMDA (0.5 M/0.5 μ L) injected into the RVMD bilaterally elicited hyperactivity walking, circling, and climbing, on d 2 post-injection with this effect lasting for the entire period of the experiment (91). Movement disorders—including tremor, rigidity, and akinesia during waking seen in human PD—were seen in the first week after NMDA injection, and disappeared by wk 2 post-injection in our NMDA-RVMD-lesioned cat (Table 1). A similar finding was also reported in the MPTP-treated cat, which never developed a permanent Parkinsonian syndrome (92). Hallucinatory behaviors in waking, such as staring ahead and ignoring moving objects, were also seen during the first wk post-NMDA injection and disappeared by wk 2 post-lesion. Sleep organization was dramatically changed after RVMD lesion in the cat (Table 1). A significant increase in waking and

a significant decrease in SWS and REM sleep were recorded on d 3 post-lesion, and continued throughout the entire 4-mo experiment (Fig. 2). Insomnia induced by RVMD lesion resulted from frequent awakening from sleep. Both the number and duration of episodes of waking were increased after RVMD lesion. However, a reduction in the number and duration of episodes of SWS and REM sleep occurred in the RVMD-lesioned cat.

Sleep architecture in the NMDA-RVMD-lesioned cat mimics that of PD in humans. Unlike our NMDA-RVMD lesion, which damaged all neuronal types and caused insomnia, specific damage to the dopaminergic neurons did not alter sleep in the chronic cat. (Pungor et al. (67) found that the MPTP-treated cat showed a decrease in REM sleep and an increase in SWS immediately after administration. Changes in the sleep-wake pattern lasted for 6-9 d and returned to baseline levels by 2 wk post-MPTP administration. 6-hydroxy-dopamine also destroys dopaminergic, nora-drenergic, and serotonergic (93-95) neurons. Intraventricular infusion of 6-hydroxydopa-mine, which reduces catecholamine (10-30% of the baseline levels) and serotonin synthesis (45-70% of the baseline levels) in different areas of the CNS (96) suppresses REM sleep with no change in SWS during a period of 15 d recording (97).

Hypothetical Neural Mechanism Involved in RVMD and VMPJ Lesion-Induced Insomnia and Hypersomnia

In contrast to the forebrain and caudal brainstem, which play a well-established role in sleep regulation, the physiological function of the midbrain in sleep has received little attention. Our studies showed that lesions in the RVMD and VMPJ produce insomnia and hypersomnia, respectively, indicating that the RVMD is related in sleep, and the VMPJ is involved in waking. In the RVMD area,

electrophysiology studies demonstrated that changes in non-dopaminergic (99), presumably GABAergic (200), neuronal activity in the ventral midbrain across the sleep cycle in the cat. Neuronal activity in the substantia nigra reticulata was also shown to be related to the occurrence of ponto-geniculo-occipital wave in REM sleep in the cat (202). Anatomically, GABAergic neurons in the RVMD project to the posterior/lateral hypothalamus (80), an area related to the control of behavioral arousal (202). In the posterior hypothalamus, an increase in GABA release was seen during SWS (203). It was also reported that microinjection of muscimol, a GABA agonist, into the posterior hypothalamus induces hypersomnia (204). Thus, we suggest that neuronal degeneration—including GABAergic neurons in the RVMD induced by NMDA injection—cause a decrease in GABA release in the posterior hypothalamus and generate insomnia, as shown in our study in the behaving cat (91). However, the cause of hypersomnia induced by VMPJ lesion remains unclear. Anatomical studies showed that neurons in the VMPJ project to the REM sleep-related areas of the PIA (79) and NMC (206) as well as to the waking-related area of the LC (207). The VMPJ also receives neuronal projections from the PIA (108). Further studies should be done to identify the sleep-related neurons and neural mechanism in the VMPJ involved in the regulation of sleep.

Hypothetical Mechanism of the Regulation of Muscle Activity in Sleep

As described in the previous section, abnormal muscle hyperactivity during sleep is reported in both PD-like and RBD patients. Postmortem histology reveals that neuronal degeneration occurs in several areas of the brainstem in both Parkinsonism and RBD. These areas—including the SN, VTA, PPN, LC, PIA, NGC, and NMC—may contribute to the modulation of muscle activity during sleep.

Lesion and electrophysiological studies demonstrated that the SN, VTA, and PPN are linked to motor activity (109-113). Activation of PPN, PIA, NGC, and NMC has also been reported to induce muscle-tone suppression (75,84,91,114,115). In contrast, activation of LC induced a facilitatory effect on motoneuronal activity (116,117). We have hypothesized that a combination of active inhibition and disfacilitation contributes to muscle-tone suppression during sleep (118). This hypothesis has been supported by our recent studies using in vivo microdialysis and HPLC techniques in the decerebrate animal. We found that release of norepinephrine and serotonin was decreased (118,119), and release of inhibitory amino acid was increased (120) in the motor nuclei during PIA and NMC stimulation-induced muscle-tone suppression. Thus, the abnormal phasic and tonic muscle activity in sleep seen in PD-like and RBD patients could result from an imbalance of neurotransmitter release onto the motoneuron pools.

Hypothetical Link between PD and RBD

Clinical evidence showed that a very high percentage of PD (50%) (21,121) patients are also diagnosed with RBD. Indeed, one study of 29 (222) and the other of 93 (33) PD-like patients showed that 38% and 52% of patients were initially diagnosed with RBD, and then developed Parkinsonism. In a study of 25 PD patients, Eisensehr et al. (122) found that two of 25 patients developed RBD and Parkinsonism simultaneously, 10 generated RBD with a median of 3 yr after diagnosis with Parkinsonism, and the remaining 13 were first diagnosed with Parkinsonism and then developed RBD. These findings strongly suggest that there might be an anatomical link between Parkinsonism and RBD. However, this association has not been explained. Since prior animal work suggested that the PIA and medial medulla were the critical substrates for RBD (70,72,73,223) and the ventral midbrain was

the key area for Parkinsonism (1,92), it was unclear why these syndromes were correlated. Our lesion studies on chronic animals may provide a clue. The VMPJ, which elicited RBD-like behavior, and RVMD, which induced PD-like sleep pattern, are anatomically adjacent to each other with a certain degree of overlap (Fig. 1). We propose that neuronal degeneration can begin in either part of the ventral brainstem, the VMPJ or RVMD, and progressively extend to the rostral or caudal part of the brainstem. RBD will develop first if the lesion starts in the VMPJ. However, Parkinsonism will appear before RBD if neuronal degeneration begins in the RVMD.

Conclusion

Most PD-related sleep disorders and RBDs are idiopathic. The onset of Parkinsonism and RBD is age-related, with both typically beginning in the sixth decade. A very high percentage of PD-like patients also suffer from RBD. Parkinsonism and RBD can appear sequentially or nearly simultaneously. Both Parkinsonism and RBD share a similar neuropathology. An abnormal concentration of dopamine transporter has been reported in the striatum in both Parkinsonism and RBD. The markers of neuronal degeneration, Lewy bodies, Lewy neurites, and α -synuclein are found in many similar areas of the CNS in both Parkinsonism and RBD. Our findings in animal studies provide an anatomical and physiological link between Parkinsonism and RBD via the ventral midbrain.

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