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# 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 $D_2$ 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 |
| SWS | decreased | increased | decreased | increased |
| 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 | ↑ phasic activity | ↑ phasic activity | ↑ phasic activity | ↑ phasic activity |
| REM sleep | ↑ phasic activity without atonia | ↑ phasic activity with and/or without atonia | ↑ phasic activity with and/or without atonia | ↑ 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 nonmonoaminergic 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 supralemniscal 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 neurons in the PPN and the vagal motor nucleus *(42)* were also reported in idiopathic PD. Similar findings are also reported for RBD. Postmortem 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

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

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 presynatpic 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*-Methl-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-aspoartate (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 paralemniscal 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).*

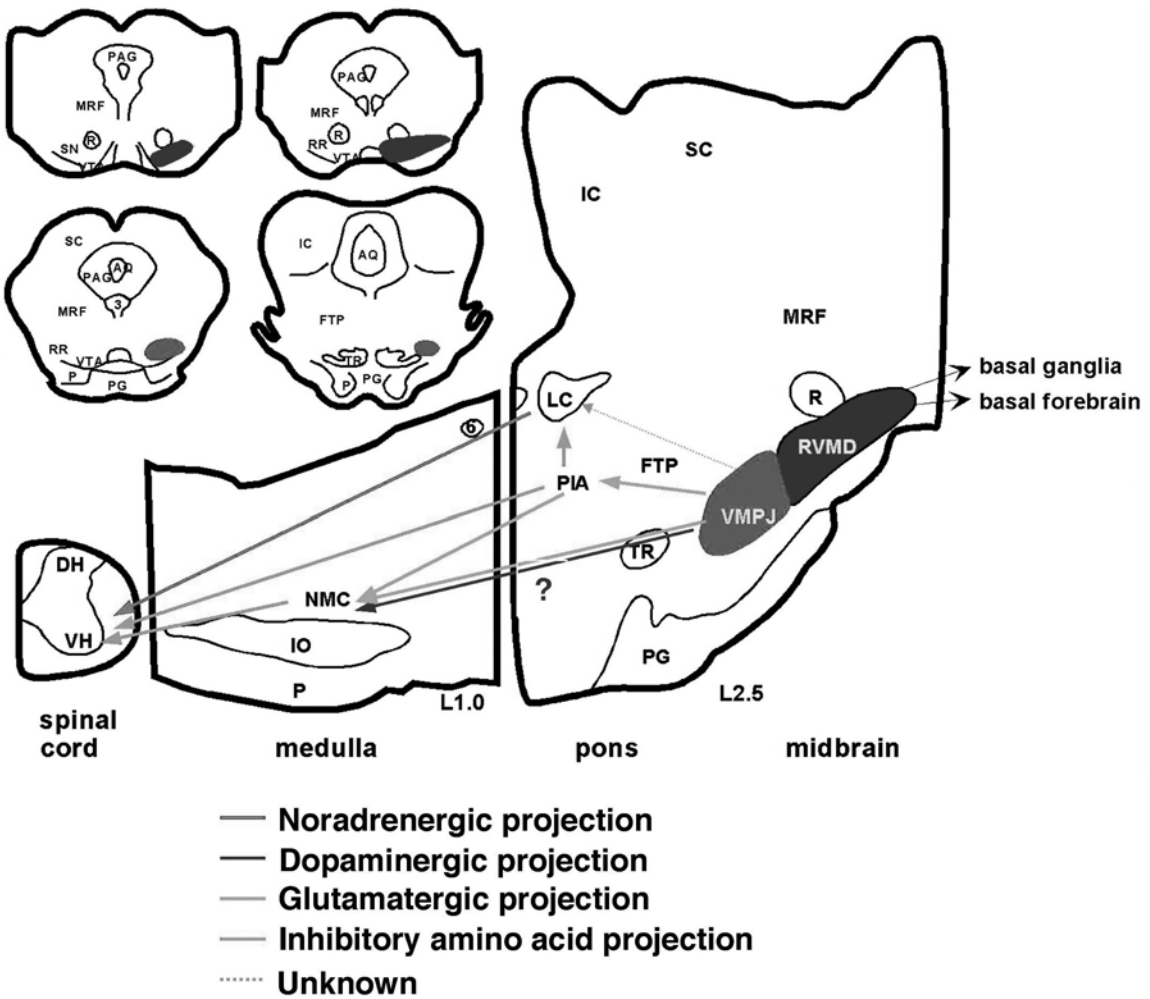


Fig. 1. Shows some of the neural circuitry in the brainstem, which we believe acts to regulate sleep motor activity. The frontal sections on the upper left show areas of the rostroventral midbrain (RVMD, dark gray area) and ventral mesopontine junction (VMPJ, light gray area). The RVMD includes the ventral 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 rostroventral 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; PG, pontine gray; R, red nucleus; SC, superior colliculus; TR, tegmental reticular nucleus; VH, ventral horn; 3, oculomotor nucleus; 6, abducens nucleus.

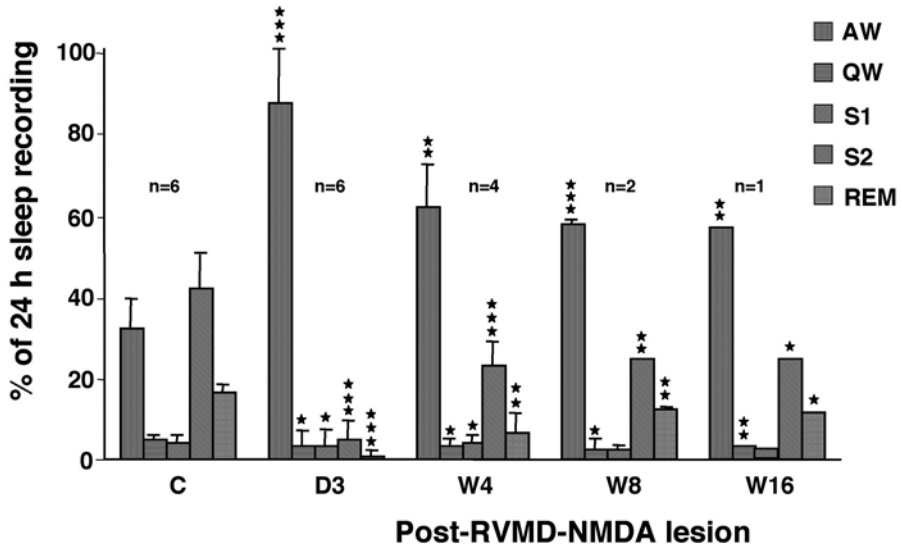


Fig. 2. Percentage of time spent in each state during the 24-h recording period before and after RVMD lesion. A significant change in each sleep-wake state occurred on d 3 post-NMDA-RVMD lesion. All stages of the sleep-wake cycle except S1 remained statistically different from the baseline control value 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 µL) 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 µL) 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-hydroxydopamine also destroys dopaminergic, noradrenergic, and serotonergic *(93–95)* neurons. Intraventricular infusion of 6-hydroxydopamine, 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 *(100),* 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 *(101).* Anatomically, GABAergic neurons in the RVMD project to the posterior/lateral hypothalamus *(80),* an area related to the control of behavioral arousal *(102).* In the posterior hypothalamus, an increase in GABA release was seen during SWS *(103).* It was also reported that microinjection of muscimol, a GABA agonist, into the posterior hypothalamus induces hypersomnia *(104).* 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 *(106)* as well as to the waking-related area of the LC *(107).* 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 *(122)* 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. *(121)* 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 *(70,71,73,123)* 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.

## References

1. German D. C., Dubach M., Askari S., Apeciale S. G., and Bowden D. M. (1988) 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonian syndrome in *Macaca fascicularis:* which midbrain dopaminergic neurons are lost? *Neuroscience* **24,** 161–174.
2. Janowsky A., Vocci F., Berger P., Angel I., Zelnik N., Kleinman J. E., et al. (1987) [$^3$H]GBR-12935 binding to the dopamine transporter is

decreased in the caudate nucleus in Parkinson's disease. *J. Neurochem.* **49,** 617–621.
3. Lee C. S., Samii A., Sossi V., Ruth T. J., Schulzer M., Holden J. E., et al. (2000) In vivo positron emission tomographic evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. *Ann. Neurol.* **47,** 493–503.
4. Varrone A., Marek K. L., Jennings D., Innis R. B., and Seibyl J. P. (2001) [(123)I]beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. *Mov. Disord.* **16,** 1023–1032.
5. Pearce R. K. B., Seeman P., Jellinger K., and Tourtellotte W. W. (1990) Dopamine uptake sites and dopamine receptors in Parkinson's disease and schizophrenia. *Eur. Neurol.* **30, Suppl 1,** 9–14.
6. Seeman P. and Niznik H. B. (1990) Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB J.* **4,** 2737–2744.
7. Cortes R., Camps M., Gueye B., Probst A., and Palacios J. M. (1989) Dopamine receptors in human: autoradiographic distribution of $D_1$ and $D_2$ sites in Parkinson syndrome of different etiology. *Brain Res.* **483,** 30–38.
8. Hierholzer J., Cordes M., Venz S., Schelosky L., Harisch C., Richter W., et al. (1998) Loss of dopamine-D2 receptor binding sites in parkinsonian plus syndromes. *J. Nucl. Med.* **39,** 954–960.
9. Tachibana M., Tanaka K., Hishikawa Y., and Kaneko Z. (1975) A sleep study of acute psychotic states due to alcohol and meprobamate addiction, in *Advances in sleep research,* Vol 2 (Weitzman E. D., ed.), New York, Spectrum, pp. 177–203.
10. Schenck C. H., Bundlie S. R., Ettinger M. G., and Mahowald M. W. (1986) Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep* **9,** 293–308.
11. Eisensehr I., Linke R., Noachtar S., Schwarz J., Gildehaus F. J., and Tatsch K. (2000) Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. *Brain* **123,** 1155–1160.
12. Albin R. L., Koeppe R. A., Chervin R. D., Consens F. B., Wernette K., Frey K. A., et al. (2000) Decreased striatal dopaminergic innervation in REM sleep behavior disorder. *Neurology* **55,** 1410–1412.
13. Tandberg E., Larsen J. P., and Karlsen K. (1998) A community-based study of sleep disorders in patients with Parkinson's disease. *Mov. Disord.* **13,** 895–899.
14. Bergonzi P., Chiurulla C., Gambi D., Mennuni G., and Pinto F. (1975) L-dopa plus dopadecarboxylase inhibitor. Sleep organization in Parkinson's syndrome before and after treatment. *Acta Neurol. Belg.* **75,** 5–10.
15. Kales A., Ansel R. D., Markham C. H., Sharf M. B., and Tan T. I. (1971) Sleep in patients with Parkinson's disease and normal subjects, prior to and following levodopa administration. *Clin. Pharmac. Ther.* **12,** 397–406.
16. Bergonzi P., Chiurulla C., Cianchettti C., and Tempesta E. (1974) Clinical pharmacology as an approach to the study of biochemical sleep mechanisms: The action of L-dopa. *Confin. Neurol.* **36,** 5–22.
17. Mouret J. (1975) Differences in sleep in patients with Parkinson's disease. *EEG Clin. Neurophysiol.* **38,** 653–657.
18. Foley D. J., Monjan A. A., Brown S. L., Simonsick E. M., Wallace R. B., and Blazer D. G. (1995) Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* **18,** 425–432.
19. Barbar S. I., Enright P. L., Boyle P., Foley D., Sharp D. S., Petrovitch H., et al. (2000) Sleep disturbances and their correlates in elderly Japanese American men residing in Hawaii. *J. Gerontol. A Biol. Sci. Med. Sci.* **55,** 406–411.
20. Schafer D. and Greulich W. (2000) Effects of parkinsonian medication on sleep. *J. Neurol.* **247 Suppl 4,** 24–27.
21. Wetter T. C., Collado-Seidel V., Pollmacher T., Yassouridis A., and Trenkwalder C. (2000) Sleep and periodic leg movement patters in drug-free patients with Parkinson's disease and multiple system atrophy. *Sleep* **23,** 361–367.
22. Ondo W. G., Dat Vuong K., Khan H., Atassi F., Kwak C., and Jankovic J. (2001) Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* **57,** 1392–1396.
23. Fish D. R., Sawyers D., Allen P. J., Blackie J. D., Lee A. J., and Marsden C. D. (1991) The effect of sleep on the dyskinetic movements of Parkinson's disease, Gilles de la Tourette syndrome, Huntington's disease, and torsion dystonia. *Arch. Neurol.* **48,** 210–214.
24. Askenasy J. J. M., Weitzman E. D., and Yahr M. D. (1985) Are periodic movements in sleep a

basal ganglia dysfunction? *J. Neural Transm.* **70,** 337–348.
25. Askenasy J. J. M. (1981) Sleep pattern in extrapyramidal disorders. *Int. J. Neurol.* **15,** 62–76.
26. Bliwise D. L., Williams M. L., Irbe D., Ansari F. P., and Rye D. B. (1997) Inter-rater reliability for identification of REM sleep in Parkinson's disease. *Sleep* **23,** 671–676.
27. Askenasy J. J. M. and Yahr M. D. (1985) Reversal of sleep disturbance in Parkinson's disease by antiparkinsonian therapy: a preliminary study. *Neurology* **35,** 527–532.
28. Schenck C. H., Hurwitz T. D., and Mahowald M. W. (1993) REM sleep behavior disorder: an update on a series of 96 patients and a review of the world literature. *J. Sleep Res.* **2,** 224–231.
29. Lapierre O. and Montplaisir J. (1992) Polysomnographic features of REM sleep behavior disorder: development of a scoring method. *Neurology* **42,** 1371–1374.
30. Schenck C. H. and Mahowald M. W. (1990) Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. *Cleveland Clin. J. Med.* **57, Suppl** S9–S23.
31. Schenck C. H., Bundlie S. R., Patterson A. L., and Mahowald M. W. (1987) Rapid eye movement sleep behavior disorder. A treatable parasomnia affecting older adults. *JAMA* **257,** 1786–1789.
32. Sforza E., Zucconi M., Petronelli R., Lugaresi E., and Cirignotta F. (1988) REM sleep behavioral disorders. *Eur. Neurol.* **28,** 295–300.
33. Olson E. J., Boeve B. F., and Silber M. H. (2000) Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain* **123,** 331–339.
34. Schenck C. H., Hopwood J., Duncan E., and Mahowald M. W. (1992) Preservation and loss of REM atonia in human idiopathic REM sleep behavior disorder (RBD): quantitative polysomnographic (PSG) analyses in 17 patients. *Sleep Res.* **21,** 16.
35. Tachibana N., Kimura K., Kitajima K., Shinde A., Kimura J., and Shibasake H. (1997) REM sleep motor dysfunction in multiple system atrophy: with special emphasis on sleep talk as its early clinical manifestation. *J. Neurol. Neurosurg. Psychiatry* **63,** 678–681.
36. Salva M.A.Q. and Guilleminault C. (1986) Olivopontocerebellar degeneration, abnormal sleep, and REM sleep without atonia. *Neurology* **36,** 576–577.
37. Tachibana N., Kimura K., Kitajima K., Nagamine T., Kimura J., and Shibasaki H. (1995) REM sleep without atonia at early stage of sporadic olivopontocerebellar atrophy. *J. Neurol. Sci.* **132,** 28–34.
38. Shimizu T., Inami Y., Sugita Y., Iijima S., Teshima Y., et al. (1990) REM sleep without muscle atonia (Stage 1-REM) and its relation to delirious behavior during sleep in patients with degenerative diseases involving the brain stem. *Jpn. J. Psychiatry Neurol.* **44,** 681–692.
39. Halliday G. M., Li Y. W., Blumbergs P. C., Joh T. H., Cotton R. G. H., Howe P.R.C., et al. (1990) Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. *Ann. Neurol.* **27,** 373–385.
40. Goto S. and Hirano A. (1991) Catecholaminergic neurons in the parabrachial nucleus of normal individuals and patients with idiopathic Parkinson's disease. *Ann. Neurol.* **30,** 192–196.
41. Patt S. and Gerhard L. (1993) A golgi study of human locus coeruleus in normal brains and in Parkinson's disease. *Neuropathol. Appl. Neurobiol.* **19,** 519–523.
42. Jellinger K. A. (1991) Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Mol. Chem. Neuropathol.* **14,** 153–197.
43. Schenck C. H., Garcia-Rill E., Skinner R. D., Anderson M. L., and Mahowald M. W. (1996b) A case of REM sleep behavior disorder with autopsy-confirmed Alzheimer's disease: postmortem brain stem histochemical analyses. *Biol. Psychiatry* **40,** 422–425.
44. Lewy F. H. (1912) Paralysis agitans. I. Pathologische anatomie, in *Handbuch der neurologie* (Lewandowsky M, ed.), Springer, Berlin, pp. 920–933.
45. Tretiakoff C. (1919) Contribution a l'etude de l'Anatomie pathologique du locus niger de soemmering avec quelques deductions relatives a la pathogenie des troubles du tonus musculaire et de la maladie de Parkinsons. These de Paris.
46. Kosaka K., Yoshimura M., Ikeda K., and Budka H. (1984) Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree – a new disease? *Clin. Neuropathol.* **3,** 185–192.
47. Ditter S. M. and Mirra S. S. (1987) Neuropathological and clinical features of Parkinson's dis-

ease in Alzheimer's disease patients. *Neurology* **37,** 754–760.
48. Uchiyama M., Isse K., Tanaka K., Yokota N., Hamamoto M., Aida S., et al. (1995) Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology* **45,** 709–712.
49. Ohama E. and Ikuta F. (1976) Parkinson's disease: distribution of Lewy bodies and monoamine neuron system. *Acta Neuropathol.* **34,** 311–319.
50. Forno L. S. (1986) The Lewy body in Parkinson's disease. *Adv. Neurol.* **45,** 35–43.
51. Turner R. S., D'Amato C. J., Chervin R. D., and Blaivas M. (2000) The pathology of REM sleep behavior disorder with comorbid Lewy body dementia. *Neurology* **55,** 1730–1732.
52. Maroteaux L., Campanelli J. T., and Scheller R. H. (1988) Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *J. Neurosci.* **8,** 2804–2815.
53. Spillantini M. G., Growther R. A., Jakes R., Hasegawa M., and Goedert M. (1998) α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc. Natl. Acad. Sci. USA* **95,** 6469–6473.
54. Hishikawa A., Hashizume Y., Yoshida M., and Sobue G. (2001) Widespread occurrence of argyrophilic glial inclusions in Parkinson's disease. *Neuropathol. Appl. Neurobiol.* **27,** 362–372.
55. Murphy D. D., Rueter S. M., Trojanowski J. Q., and Lee V.M.Y. (2000) Synucleins are developmentally expressed, and α-synuclein regulates the size of the presynaptic vesicular pool in primary hippocampal neurons. *J. Neurosci.* **20,** 3214–3220.
56. Jensen P. H., Nielsen M. S., Jakes R., Dotti C. G., and Goedert M. (1998) Binding of alpha-synuclein to brain vesicles is abolished by familial Parkinson's disease mutation. *J. Biol. Chem.* **273,** 26,292–26,294.
57. Baba M., Nakajo S., Tu P. H., Tomita T., Nakaya K., Lee V. M. Y., et al. (1998) Aggregation of α-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am. J. Pathol.* **152,** 879–884.
58. Wakabayashi K., Matsumoto K., Takayama K., Yoshimoto M., and Takahashi H. (1997) NACP, a presynaptic protein, immunoreactivity in Lewy bodies in Parkinson's disease. *Neurosci. Lett.* **239,** 45–48.
59. Takeda A., Mallory M., Sundsmo M., Honer W., Hansen L., and Masliah E. (1998) Abnormal accumulation of NACP/α-synuclein in neurodegenerative disorders. *Am. J. Pathol.* **152,** 367–372.
60. Braak H., Rub U., Sandmann-Keil D., Gai W. P., de Vos R. A. I., Jansen E. N. H., et al. (2000) Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. *Acta Neuropathol.* **99,** 489–495.
61. Braak H., Sandmann-Keil D., Gai W. P., and Braak E. (1999) Extensive axonal Lewy neurites in Parkinson's disease: a novel pathological feature revealed by α-synuclein immunohistochemistry. *Neurosci. Lett.* **265,** 67–69.
62. Namura I., Douillet P., Sun G. J., Pert A., Cohen R. M., and Chiueh C. C. (1987) $MPP^4$ (1-methyl-4-phenylpyridine) is a neurotoxin to dopamine-, norepinephrine- and serotonin-containing neurons. *Eur. J. Pharmacol.* **136,** 31–37.
63. Ballard P. A., Tetrud J. W., and Langston J. W. (1985) Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): 7 cases. *Neurology* **35,** 949–956.
64. Davis G. C., Williams A. C., Markey S. P., Ebert M. H., Caine E. D., Reichert C. M., et al. (1979) Chronic parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiat. Res.* **1,** 249–254.
65. Forno L. S., Langston J. W., DeLanney L. E., Irwin I., and Ricaurte G. A. (1986) Locus ceruleus lesions and eosinophilic inclusions in MPTP-treated monkeys. *Ann. Neurol.* **20,** 49–55.
66. Kowall N. W., Hantrye P., Brouillet E., Beal M. F., McKee A. C., and Ferrante R. J. (2000) MPTP induces alpha-synuclein aggregation in the substantia nigra of baboons. *Neuroreport* **11,** 211–213.
67. Pungor K., Papp M., Kekesi K., and Juhasz G. (1990) A novel effect of MPTP: the selective suppression of paradoxical sleep in cats. *Brain Res.* **525,** 310–314.
68. Jouvet M. and Delorme J. F. (1965) Locus coeruleus et sommeil paradoxal. *C R Seances Soc. Biol. Fil.* **159,** 895–899.
69. Henley K. and Morrison A. R. (1974) A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat. *Acta Neurobiol. Exp.* **34,** 215–232.

70. Schenkel E. and Siegel J. M. (1989) REM sleep without atonia after lesions of the medial medulla. *Neurosci. Lett.* **98,** 159–165.
71. Shouse M. N. and Siegel J. M. (1992) Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. *Brain Res.* **571,** 50–63.
72. Holmes C. J. and Jones B. E. (1994) Importance of cholinergic, GABAergic, serotonergic and other neurons in the medial medullary reticular formation for sleep-wake states studied by cytotoxic lesions in the cat. *Neuroscience* **62,** 1179–1200.
73. Hendricks J. C., Morrison A. R., and Mann G. L. (1982) Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. *Brain Res.* **239,** 81–105.
74. Schenck C. H. and Mahowald M. W. (1996) REM sleep parasomnias. *Neurol. Clin.* **14,** 697–720.
75. Lai Y. Y. and Siegel J. M. (1990) Muscle tone suppression and stepping produced by stimulation of midbrain and rostral pontine reticular formation. *J. Neurosci.* **10,** 2727–2734.
76. Lai Y. Y. and Siegel J. M. (1997) Brainstem-mediated locomotion and myoclonic jerks. I. Neural substrates. *Brain Res.* **745,** 257–264.
77. Dahlstrom A. and Fuxe K. (1964) Evidence for the existence of monoamine-containing neurons in the central nervous system. *Acta Physiol. Scand.* **62 Suppl. 232,** 5–78.
78. Wiklund L., Leger L., and Persson M. (1981) Monoamine cell distribution in the cat brain stem. A fluorescence histochemical study with quantification of indolaminergic and locus coeruleus cell groups. *J. Comp. Neurol.* **203,** 613–647.
79. Lai Y. Y., Clements J. R., and Siegel J. M. (1993) Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry. *J. Comp. Neurol.* **336,** 321–330.
80. Ford B., Holmes C. J., Mainville L., and Jones B. E. (1995) GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. *J. Comp. Neurol.* **363,** 177–196.
81. Stamp J. A. and Semba K. (1995) Extent of colocalization of serotonin and GABA in the neurons of the rat raphe nuclei. *Brain Res.* **677,** 39–49.
82. Vertes R. P. and Crane A. M. (1997) Distribution, quantification, and morphological characteristics of serotonin-immunoreactive cells of the supralemniscal nucleus (B9) and pontomesencephalic reticular formation in the rat. *J. Comp. Neurol.* **378,** 411–424.
83. Magoun H. W. and Rhines R. (1946) An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.* **9,** 165–171.
84. Lai Y. Y., Siegel J. M., and Wilson W. J. (1987) Effect of blood pressure on medial medulla-induced muscle atonia. *Am. J. Physiol.* **252,** H1249–H1257.
85. Hajnik T., Lai Y. Y., and Siegel J. M. (2000) Atonia-related regions in the rodent pons and medulla. *J. Neurophysiol.* **84,** 1942–1948.
86. Lai Y. Y. and Siegel J. M. (1991) Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. *J. Neurosci.* **11,** 2931–2937.
87. Lai Y. Y. and Siegel J. M. (1992) Corticotropin-releasing factor mediated muscle atonia in pons and medulla. *Brain Res.* **575,** 63–68.
88. Lai Y. Y. and Siegel J. M. (1997) Brainstem-mediated locomotion and myoclonic jerks. II. Pharmacological effects. *Brain Res.* **745,** 265–270.
89. Lai Y. Y., Shalita T., Kodama T., and Siegel J. M. (2001) Neurotoxic lesion of the ventral mesopontine junction induces muscle hyperactivity during sleep. *Soc. Neurosci. Abstr.* Vol 27, Program # 296.2.
90. Lai Y. Y., Shalita T., Wu J. P., and Siegel J. M. (2002) Neurotoxic lesion of the ventral mesopontine junction induces hypersomnia and muscle hyperacitivity during sleep—an animal model of PLMD and RBD. *Sleep* **25,** A62.
91. Lai Y. Y. and Siegel J. M. (1999) Muscle atonia in REM sleep, in *Rapid eye movement sleep.* (Mallick B. N. and Inoue S., eds.), Narosa Pub. House, New Delhi, pp. 69–90.
92. Schneider J. S., Yuwiler A., and Markham C. H. (1986) Production of a Parkinson-like syndrome in the cat with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): behavior, histology, and biochemistry. *Exp. Neurol.* **91,** 293–307.
93. Understedt U. (1968) 6-hydroxydopamine induced degeneration of central monoamine neurons. *Eur. J. Pharmacol.* **5,** 107–110.

94. Breese G. R. and Taylor T. D. (1970) Effects of 6-hydroxydopamine on brain norepinephrine and dopamine: evidence for selective degeneration of catecholamine neurons. *J. Pharmacol. Exp. Ther.* **174,** 413–420.
95. Sawynok J. and Reid A. (1996) Neurotoxin-induced lesions to central serotonergic, noradrenergic and dopaminergic systems modify caffeine-induced antinociception in the formalin test and locomotor stimulation in rats. *J. Pharmacol. Exp. Ther.* **277,** 646–653.
96. Petitjean F., Laguzzi R., Sordet F., Jouvet M., and Pujol J. F. (1972) Effects de l'injection intraventriculaire de 6-hydroxydopamine. I. Sur les monoamines cerebrales du chat. *Brain Res.* **48,** 281–293.
97. Laguzzi R., Petitjean F., Pujol J. F., and Jouvet M. (1972) Effects de l'injection intraventriculaire de 6-hydroxydopamine. II Sur le cycle veille-sommeils du chat. *Brain Res.* **48,** 295–310.
98. Miller J. D., Farber J., Gatz P., Roffwarg H., and German D. C. (1983) Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and waking in the rat. *Brain Res.* **273,** 133–141.
99. Steinfels G. F., Heym J., Strecker R. E., and Jacobs B. L. (1983) Behavioral correlates of dopaminergic unit activity in freely moving cats. *Brain Res.* **258,** 217–228.
100. Otterson O. P. and Storm-Mathisen J. (1984) Neurons containing or accumulating transmitter amino acids. In: Handbook of chemical neuroanatomy, (Bjoklund A., and Hokfelt T., Kuhar M. J., eds.), Amsterdam: Elsevier, pp. 141–245.
101. Datta S., Curro Dossi R., Pare D., Oakson G., and Steriade M. (1991) Substantia nigra reticulata neurons during sleep-waking states: relation with ponto-geniculo-occipital waves. *Brain Res.* **566,** 344–347.
102. Szymusiak R. and McGinty D. (1986) Sleep-related neuronal discharge in the basal forebrain of cats. *Brain Res.* **258,** 217–228.
103. Nitz D. and Siegel J. S. (1996) GABA release in posterior hypothalamus across sleep-waking cycle. *Am. J. Physiol.* **271,** R1707–R1712.
104. Lin J. S., Sakai K., Vanni-Mercier G., and Jouvet M. (1989) A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. *Brain Res.* **479,** 225–240.
105. Lai Y. Y., Shalita T., Hajnik T., Wu J. P., Kuo J. S., Chia L. G., et al. (1999) Neurotoxic N-methyl-D-aspartate lesion of the ventral midbrain and mesopontine junction alters sleep wake organization. *Neuroscience* **90,** 469–483.
106. Lai Y. Y., Clements J. R., Wu X. Y., Shalita T., Wu J. P., Kuo J. S., et al. (1999) Brainstem projections to the ventromedial medulla in cat: retrograde transport horseradish peroxidase and immunohistochemical studies. *J. Comp. Neurol.* **408,** 419–436.
107. Luppi P. H., Aston-Jones G., Akaoka H., Chouvet G., and Jouvet M. (1995) Afferent projections to the rat locus coeruleus demonstrated by retrograde and anterograde tracing with cholera-toxin B subunit and *Phaseolus vulgaris* Leucoagglutinin. *Neuroscience* **65,** 119–160.
108. Vertes R. P. and Martin G. F. (1988) Autoradiographic analysis of ascending projections from the pontine and mesencephalic reticular formation and the median raphe nucleus in the rat. *J. Comp. Neurol.* **275,** 511–541.
109. Understedt U. and Arbuthnott G. W. (1970) Quantitative recording of rotational behavior in rats after 6-hydroxydopamine lesions of the nigrostriatal doapmine system. *Brain Res.* **24,** 485–493.
110. Carey R. J. (1986) Relationship of changes in spontaneous motor activity to spontaneous circling in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra. *Exp. Neurol.* **92,** 591–600.
111. Dunbar J. S., Hitchcock K., Latimer M., Rugg E. L., Ward N., and Winn P. (1992) Excitotoxic lesions of the pedunculopontine tegmental nucleus of the rat. II. Examination of eating and drinking, rotation, and reaching and grasping following unilateral ibotenate or quinolinate lesions. *Brain Res.* **589,** 194–206.
112. Kiyatkin E. A. and Rebec G. V. (1998) Heterogeneity of ventral tegmental area neurons: single-unit recording and iontophoresis in awake, unrestrained rats. *Neuroscience* **85,** 1285–1309.
113. Gulley J. M., Kuwajima M., Mayhill E., and Rebec G. V. (1999) Behavior-related changes in the activity of substantia nigra pars reticulata neurons in freely moving rats. *Brain Res.* **845,** 68–76.
114. Kelland M. D. and Asdourian D. (1989) Pedunculopontine tegmental nucleus-induced inhibition of muscle activity in the rat. *Behav. Brain Res.* **34,** 213–234.

115. Lai Y. Y. and Siegel J. M. (1988) Medullary regions mediating atonia. *J. Neurosci.* **8,** 4790–4796.
116. Fung S. J. and Barnes C. D. (1981) Evidence of facilitatory coerulospinal action in lumbar motoneurons of cats. *Brain Res.* **216,** 299–311.
117. Lai Y. Y., Strahlendorf H. K., Fung S. J., and Barnes C. D. (1989) The actions of two monoamines on spinal motoneurons from stimulation of the locus coeruleus in the cat. *Brain Res.* **484,** 268–272.
118. Lai Y. Y., Kodama T., and Siegel J. M. (2001) Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: an in vivo microdialysis study. *J. Neurosci.* **21,** 7384–7391.
119. Lai Y. Y., Kodama T., and Siegel J. M. (2000) Suppression of norepinephrine release is linked to the rostral dorsomedial but not ventromedial medulla induced atonia. *Soc. Neurosci. Abstr.* **26,** 693.
120. Kodama T., Lai Y. Y., and Siegel J. M. (2000) Glycine release is increased in the ventral horn and hypoglossal motoneuron pools during rostromedial medulla-induced atonia. *Soc. Neurosci. Abstr.* **26,** 693.
121. Eisensehr I., v Lindeiner H., Jager M., and Noachtar S. (2001) REM sleep behavior in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography? *J. Neurol. Sci.* **186,** 7–11.
122. Schenck C. H., Bundlie S. B., and Mahowald M. W. (1996) Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. *Neurology* **46,** 388–393.
123. Sanford L. D., Morrison A. R., Mann G. L., Harris J. S., Yoo L., and Ross R. J. (1994) Sleep pattering and behaviour in cats with pontine lesions creating REM without atonia. *J. Sleep Res.* **3,** 233–240.
124. Lavoie B., Smith Y., and Parent A. (1989) Dopaminergic innervation of the basal ganglia in the squirrel monkey as revealed by tyrosine hydroxylase immunohistochemistry. *J. Comp. Neurol.* **289,** 36–52.
125. Fallon J. H. and Moore R. Y. (1978) Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. Comp. Neurol.* **180,** 545–580.
126. Vertes R. P. (1988) Brainstem afferents to the basal forebrain in the rat. Neuroscience **24,** 907–935.