Chapter 7

Lesions Associated with Sleep Disturbances

Marcus M. Unger, Wolfgang H. Oertel, Thomas C. Thannickal, Yuan-Yang Lai, and Jerome M. Siegel

In: Non-dopamine lesions in Parkinson's disease. Glenda M. Halliday, Roger A. Barker and Dominic B. Rowe (Eds), Oxford, 2010

Introduction

Sleep disturbances are frequently reported complaints in patients with Parkinson's disease (PD) and are seen throughout all stages of the illness. On the one hand, certain sleep disorders can emerge already at preclinical stages, heralding the emergence of PD. On the other hand, disease progression (as assessed by Hoehn and Yahr stage) has been shown to be associated with a worsening of sleep-related disturbances.' The relevance of sleep disturbances as a non-motor symptom for PD patients is illustrated by the fact that the subjective quality of sleep in PD patients is not only poorer compared to healthy subjects, but also compared td patients with other neurodegenerative disorders, e.g. Alzheimer's disease.[2]

The spectrum of sleep-related symptoms seen in PD patients comprises a variety of disorders, including disturbances that occur during daytime, like excessive daytime sleepiness (EDS) and sleep attacks (SA), as well as disturbances that occur at night, e.g. nocturnal recurrence of PD motor symptoms (akinesia, painful cramps), nocturia, vivid dreams, REM sleep behavior disorder (RBD), restless legs syndrome (RLS), periodic limb movements during sleep (PLMS), and others.

The etiology of sleep disturbances in PD is most likely multifactorial and in part due to the neurodegenerative process (affecting centers that

regulate sleep and wakefulness), the pharmacological therapy, and the inter-individual susceptibility. The impact of drug intervention, especially dopaminergic therapy, on sleep disturbances in PD is debatable, as sleep disturbances are also seen in drug-naïve PD patients.[3]

The pathoanatomicial model of PD proposed by Braak and colleagues[4,5] provides a neuropathological correlate for the observation that sleep disturbances can already occur at preclinical stages of PD. According to Braak's scheme, the lower brainstem (pons and medulla) involved in the regulation of sleep and wakefulness is affected early by the neurodegenerative process, i.e. prior to degeneration at the midbrain level and the occurrence of motor impairments.

This chapter will give an overview of sleep-related disturbances in PD patients with respect to epidemiology, clinical presentation, therapeutic options and (where known) the respective underlying pathophysiology.

Sleep-related Disturbances in PD Occurring During Daytime

Excessive Daytime Sleepiness (EDS)

Excessive daytime sleepiness (EDS) as a recurrent compulsion to sleep during daytime is frequently seen in PD patients. A nationwide face-to-face survey on excessive daytime sleepiness (defined as an Epworth Sleepiness Scale (ESS) score _10) in 1625 PD patients (most of them treated with dopaminergic drugs) in France revealed a prevalence of 29% for EDS.' The etiology of EDS in PD remains unclear and disputed: involvement of brainstem structures that regulate sleep and wakefulness by the neurodegenerative process, untoward effects of the dopaminergic medication, as well as an interaction between the first and the latter are discussed. Daytime sleepiness in PD has been reported to be associated with nigrostriatal dopaminergic degeneration as visualized by presynaptic dopamine transporter imaging.[?] Yet these data do not allow conclusions as to whether the dopaminergic nigrostriatal degeneration represents the pathoanatomical correlate for EDS or is just an epiphenomenon.

The Honolulu-Asia aging study found that EDS in men aged 71 to 93 years without signs of PD or dementia was associated with a threefold excess in the risk of developing PD,[8] arguing that EDS might be a premotor feature of evolving PD rather than a medication-induced phenomenon. Yet, another study found that the prevalence for EDS does not differ between drug-naïve PD patients and age and sex-matched healthy controls.[9] In a follow-up of the same cohort one year post initiation of a dopaminergic therapy, Epworth Sleepiness Scale (ESS) scores significantly

increased,[10] arguing for a pharmacological effect. Another study showed that frequency rates of EDS increase with time."

A poor quality of sleep (sleep fragmentation, arousals, etc.) and sleep-disordered breathing may also account for EDS in PD patients. Yet, Amulf and colleagues found that these factors did not correlate with sleepiness in PD patients [12] and that the dose of dopaminergic treatment did not contribute to sleepiness, but conversely showed vigilance-enhancing effects. This is in contrast to other studies which found that dopamine receptor agonists contribute to daytime sleepiness."[,13]

In conclusion, the etiology of EDS in PD most likely is multifactorial and the contribution of (dopaminergic) drugs to EDS depends on an inter-individual susceptibility. Treatment of EDS in PD therefore includes (despite controversial data) reduction of dopamine receptor agonist treatment and screening for (treatable) nocturnal sleep disturbances (e.g. obstructive sleep apnea) that potentially can result in sleep fragmentation. If these measures are not sufficiently successful and the patient's quality of life is severely affected by EDS, stimulants like modafinil might be considered as a therapeutic option. [}4-16]

A Narcolepsy-like Phenotype in PD?

EDS is also one of the chief complaints in another neurological disorder, i.e. narcolepsy. Arnulf and colleagues reported a narcolepsy-like phenotype (excessive daytime sleepiness, shortened sleep latency and sleep-onset REM periods) in PD patients with EDS.[12,17] In addition, daytime hallucinations in these patients showed a coincidence with short REM sleep intrusions during periods of wakefulness; also the presence of Lewy body pathology in the subcoeruleus nucleus (which is known to control REM sleep) in a PD patient with hallucinations suggests that visual hallucinations in PD might reflect a narcolepsy-like REM sleep disorder:[8] Other authors dispute a common pathophysiological basis for narcolepsy and PD [19] and refer to the conflicting data concerning hypocretin (orexin) CSF levels in PD."-[23] Yet, recently published post-mortem data demonstrated • hypocretin cell loss in PD: decreased hypocretin-1 tissue concentrations in the prefrontal cortex and a stage-dependent loss of hypothalamic hypocretin neurons were shown by Fronczek et al and Thannickal et a1,[24,25] arguing again for some common pathological alterations in PD and narcolepsy.

Sleep Attacks (SA)

The issue of sleep attacks (SA) in PD has raised much attention because of the potential danger of falling asleep while driving.[26] Sleep attacks in PD are defined as an inappropriate sudden onset of an overwhelming, irresistible sleepiness occurring without warning and preventing the patient from

taking appropriate measures to protect himself.[27] These SA are frequently associated with EDS, but can also occur in the absence of EDS.[28]

Sleep attacks have initially been described in PD patients on dopamine receptor agonist treatment,[29] but are also reported under levodopa monotherapy (showing a dose dependency),[30] and after initiation of entacapone.[31-33] These observations argue that SA are not exclusively due to dopamine receptor agonists but can be induced by any dopaminergic drug and that SA are related to the bioavailability of dopaminergic drugs and total dopaminergic load rather than to a single class of substances.

The absence of SA in patients treated with dopamine receptor agonists for restless legs syndrome, the fact that SA in PD can also occur at low doses of dopaminergic treatment in some patients (i.e. the lack of a clear dose effect correlation), and the lack of a clear temporal association with the introduction (specifically elevation of the dosage) of certain drugs argues for a susceptibility rather than a sole drug effect or disease-intrinsic mechanisms.[34] Genetic factors may also contribute to the occurrence of SA in PD patients: polymorphisms in the dopamine D2 and D4 receptor genes and polymorphisms in the preprohypocretin gene have been described.[35-37]

A cross-sectional study in 2952 PD patients revealed SA in 177 subjects (-6%). Sleep attacks occurred with all types of DA with no significant differences between ergot and non-ergot dopamine receptor agonists. Yet the risk for sleep attacks increased when comparing levodopa mono-therapy to dopamine receptor agonist monotherapy and to a combination of levodopa *and* dopamine receptor agonist therapy,[38] arguing again that the total degree of dopaminergic stimulation contributes to SA. Another study in 6620 PD patients found that younger patients (below the age of 70 years) taking non-ergot dopamine receptor agonists are more susceptible to experience SA, yet medication was less effective in predicting SA than other factors (age, male gender, disease duration, etc.),[39] arguing for a multifactorial pathogenesis.

A cross-sectional case-control study in PD patients and healthy volunteers showed that the same proportion of PD patients and controls reported episodes of sleep attacks (approx. 1 /3). Nevertheless, sleep attacks occurred more frequently in PD, especially during situations requiring attention. In this study, the most consistent factor associated with sleep attacks was the duration of levodopa therapy.[40]

In conclusion, PD patients should be routinely asked about the presence of SA and be informed about the potential risk of falling asleep at the wheel. It is disputed whether the Epworth Sleepiness Scale (ESS) is suitable to screen for SA (poor positive predictive value, but good negative predictive value).[40] If SA occur under dopamine receptor agonist

treatment, a switch to another dopamine receptor agonist or a reduction of the dosage should be considered (if possible).

Sleep-related Disturbances Occurring at Night time

Sleep Apnea Syndrome (SAS)

Diederich et al found a frequency of sleep apnea syndrome (SAS) of 43% in an unselected sample of 49 PD patients.' Interestingly (in contrast to what is known for SAS in the general population), SAS in PD was not associated with obesity, and PD patients maintained a more favorable respiratory profile than non-PD SAS controls (matched in terms of age, gender and apnea/hypopnea index). In sum, in this study SAS was not a major cause for sleep fragmentation and SAS in PD seems to have a different profile in terms of polysomonographic and respiratory parameters. Thus, it is doubtful whether SAS in PD contributes to EDS. Continuous positive airway pressure (CPAP) treatment should be initiated if indicated by the respiratory profile seen in the cardio-respiratory polysomnography.

Insomnia, Vivid Dreams and (Nocturnal) Hallucinations

Stimulatory effect of drugs used to treat PD, especially amantadine and MAO-B-inhibitors (amphetamine metabolites), can induce insomnia. In addition, these drugs and also dopamine receptor agonists can cause vivid dreams and nocturnal hallucinations. Rescheduling, reduction, or (in more severe cases) discontinuation of these drugs should be considered to overcome these problems. In the case of severe (nocturnal) hallucinations that do not respond to the aforementioned measures, addition of atypical neuroleptic drugs (especially clozapine) is indicated. In order to treat insomnia, patients should also be informed about sleep hygiene, specifically how to maintain the circadian rhythm (bright light during the day, darkness during the night, use bedroom only for sleep, etc.). Any inappro:- priate aggressive nocturnal behavior in PD patients should also prompt checking for REM sleep behavior disorder (RBD).

REM Sleep Behavior Disorder (RBD)

REM sleep behavior disorder (RBD) is a male-predominant parasomnia that was scientifically described for the first time in 1986 by Schenck and colleagues. RBD presents with dream-enacting motor behaviors and speech during REM sleep.' Most patients with RBD seek medical help when their dream-enactments result in physical injury to themselves or their bed partner. A diagnosis of RED is established by the typical history

of dream enactments (including information from the patient's spouse/ caregiver about the sleep behavior) and loss of (the physiological) muscle atonia during REM sleep (documented by video-polysomnography).

In the absence of a concomitant neurological disorder, RBD is termed idiopathic **RBD (iRBD),** which has been shown to be a risk marker for subsequent development of neurodegenerative disorders, especially PD. In 1996, Schenck and colleagues reported that 11 out of 29 patients (i.e. 38%) initially diagnosed to suffer from iRBD eventually developed a parkinsonian syndrome, with a mean follow-up of 12.7 years.'" On a second follow-up 7 years later, 19 of the initial 29 iRBD patients (i.e. 65%) presented with a parkinsonian syndrome, dementia or both diseases. Cross-sectional studies have shown that approximately one-third of PD patients exhibit RBD when examined by V-PSG." Pachetti and colleagues also screened PD patients for RBD and found a similar prevalence of RBD (26.6%). Retrospectively, approximately one-third developed RBD before, and two-thirds after, diagnosis of PD.[45] The largest retrospective study investigating **RBD** and concomitant diseases has been published by Olsen and colleagues: among 93 patients with **RBD** 53 presented with a concomitant neurological disorder, 25 of these 53 patients had PD. With a closer look at the 25 patients with **RBD** and PD, it was found that RBD developed before PD in 13 patients, simultaneously in 2 patients and after diagnosis of PD in 10 patients.' It is unclear which mechanisms are responsible for the occurrence of **RBD either** before or after the manifestation of PD. One possible explanation for the divergent observations concerning the sequence of both diseases might be that in cases where RBD is reported and/or identified only in the course of PD there is a lack of sufficient investigation for subclinical stages at earlier time points. Interestingly, RBD (but also sleep disorders in general) constitute a predictor for emerging hallucinations in PD.[45.47.48]

The first post mortem studies in **RBD** patients described degeneration of monoaminergic (noradrenergic, dopaminergic, serotonergic) neurons and the presence of Lewy bodies in the brainstem and intracellular alphasynuclein inclusions."[8,49] The pattern of lesions was very similar to the brainstem pathology seen in very early PD according to the neuropathologcial staging of PD proposed by Braak.[4] According to Braak's neuropathological staging, lesions in brainstem structures occur before the dopaminergic nigrostriatal pathway becomes affected. Braak's post mortem data support the assumption that RBD and PD are closely linked and even more, that from a neuroanatomical point of view, **RBD** should precede PD.

While routine imaging with magnetic resonance imaging (MRI) or computed tomography (CT) rarely detects or reveals brainstem pathology

in RBD patients,[46] a reduced presynaptic striatal dopamine transporter uptake was shown using single photon emission computed tomography (SPECT) in RBD patients without motor symptoms of PD.[5°] This finding and the proof of an olfactory dysfunction in RBD patients demonstrated by Stiasny-Kolster and colleagues[51] is in agreement with Braak's patho-anatomical staging.[4] According to Braak's model (Fig. 7-1), impaired olfactory function represents stage 1 of PD (Lewy body pathology in the olfactory bulb), the presence of PD stage 2 (Lewy body pathology is also seen in the medulla and pons), and the clinical manifestation of classical neurological signs such as akinesia, tremor or rigidity represents stage 3 PD (Lewy body pathology affects the midbrain level).

Hitherto, no causal therapeutical strategies for RBD have been available. Yet, the physical injuries that can result from the often violent behaviors during sleep and the morbidity associated with chronic sleep disruption, stress the need for a symptomatic therapy. Clonazepam (0.5 to 1 mg per night) is effective in most patients and is the drug of choice. In cases where the response to clonazepam is incomplete or when clonazepam is contraindicated, melatonin (0.5 to 12 mg per night) seems to be an alternative treatment option.[52-54] Boeve and colleagues have shown the effectiveness of melatonin specifically in patients with accompanying neurodegenerative disorders (n=14).[55] Improvement of RBD with oral administration of melatonin [52-55] as well as positive effects of melatonin on the subjective quality of sleep and even on motor function in PD patients[56] argue for involvement of the melatonin system. Melatonin has antioxidant properties that could modify the neurodegenerative process, but the short-term response directly after initiation of melatonin argues for a more direct action of melatonin. Interestingly, and in part controversial to the aforementioned, bright light therapy (melatonin antagonism) has also shown beneficial effects in PD.[57,58] As RBD is often seen in the context of evolving PD, there have also been trials with levodopa and dopamine receptor agonists in a small group of patients. Tan and colleagues reported improvement of RBD symptoms when patients with early PD were treated with levodopa.[59] Ozekmekci and co-workers have shown that PD patients with RBD require higher levodopa doses to regain motor abilities compared to PD patients without RBD and that levodopa treatment cannot prevent the occurrence of RBD.[6°] Pramipexole, a dopamine D2/D3-receptor agonist, has been shown to relieve RBD-related sleep disturbing symptoms.' However, pramipexole was not able to alter phasic EMG activity during REM sleep—when used as a possible quantitative marker of disease severity.' Also, cholinesterase inhibitors have been shown to relieve RBD symptoms in single patients. These drugs putatively modify the

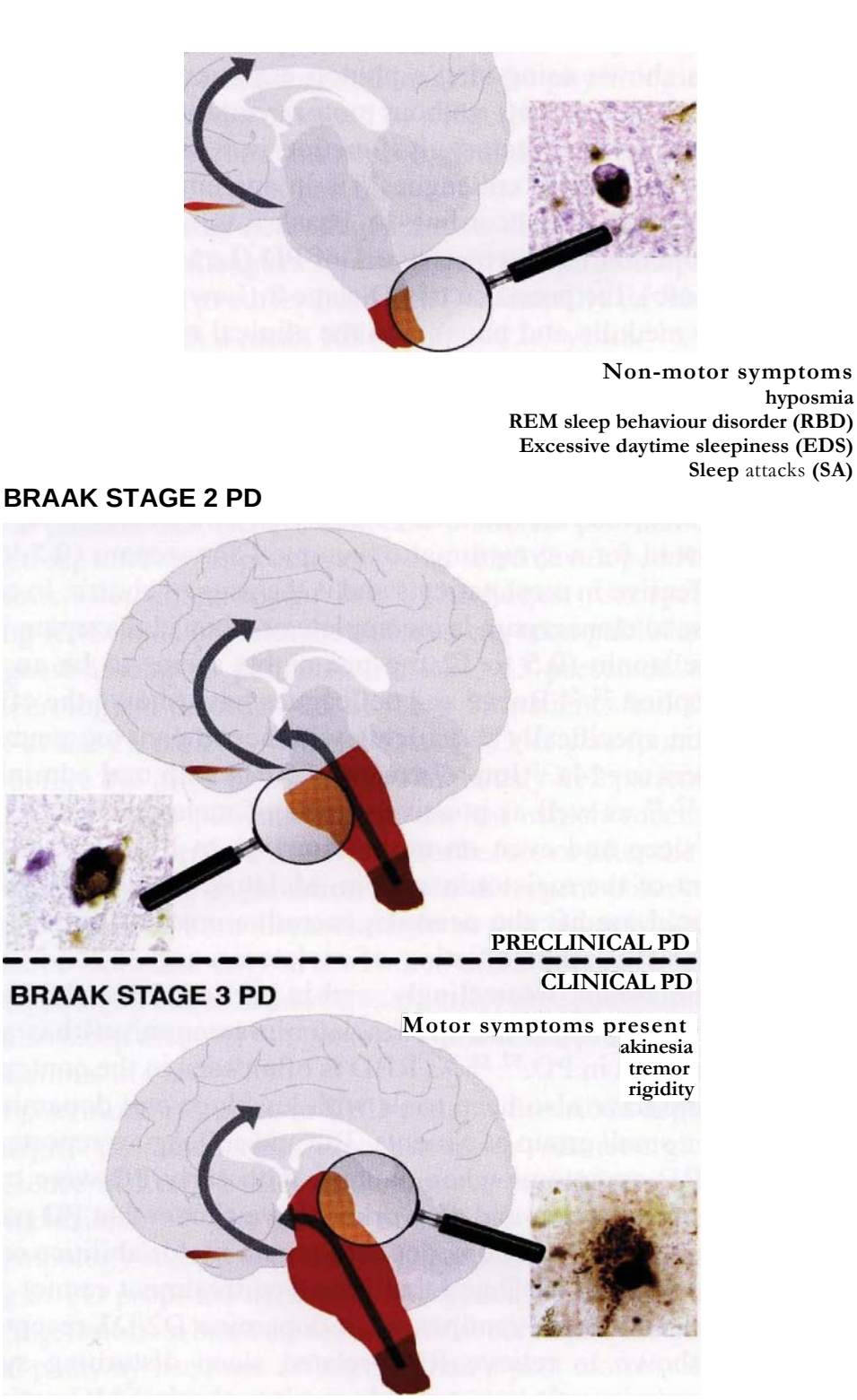

Figure 7-1. The distribution of Lewy body (LB) pathology in preclinical (premotor) and early clinical stages of PD according to Braak's pathoanatomical model. **In** preclinical stages (Braak stage 1 and 2) LB pathology in the brainstem (pons, medulla) and the olfactory bulb could explain the occurrence of sleep disorders and other non-motor symptoms (hyposmia, autonomic dysfunction, etc.). Upon involvement of the midbrain level with its nigrostriatal projections, the PD-typical motor symptoms occur and allow the clinical diagnosis of PD.

neuronal activity of the pedunculopontine nucleus.[63] Yet clinical trials that prove the effectiveness of any of the mentioned drugs in a double-blind placebo-controlled study remain to be initiated. Beside the pharmacological management, patients should be instructed about measures preventing physical injuries during RBD episodes (closing windows before sleep, removing sharp and dangerous objects from around the bed).

For experimental research, several animal models of RBD have been developed. Bilateral pontine tegmental lesions have been shown to provoke an RBD-like phenotype[64] and also circumscribed lesions in the ventral mesopontine junction (VMPJ) in cats resulted in a RBD-like phenotype.' There are a number of other animal models demonstrating that the lesion of brainstem structures can result in RBD.[66,67] Hence, brain-stem nuclei in the pons and medulla are thought to be responsible for RBD.[66] This notion is supported by case reports of patients with defined structural brainstem lesions who developed RBD.[68•69] For example, even a minimal ischemic pontine lesion has been shown to be sufficient to cause RBD.[7°] Mazza et al" also demonstrated abnormal cerebral blood flow in the pons in RBD patients, using 99mTc-ethylene cysteinate dieter SPECT technique. This observation strongly supports the assumption that the localization of a lesion, rather than its histological type is responsible for manifestation of RBD.

In PD, degeneration of cholinergic neurons in the pedunculopontine nucleus[72] as well as Lewy body pathology in the locus coeruleus[49] might be anatomical correlates of RBD. Post-mortem analysis of the brain of a patient with RBD who eventually developed cognitive decline and parkinsonism revealed marked neuronal loss in the locus coeruleus and substantia nigra—regions that may inhibit cholinergic neurons in the pedunculopontine nucleus (mediating atonia during REM sleep).[73]

In sum, RBD in (evolving) PD most likely reflects brainstem lesions in the medulla and pons. The presumed pathophysiology is that these lesions cause a net reduction in the inhibition of spinal motoneurons that are normally suppressed by a complex interaction of brainstem nuclei during REM sleep, thereby preventing motor activity during REM sleep.[74-76]

Sleepwalking

A sleep disorder that can clinically mimic RBD is sleepwalking. Adult-onset sleepwalking is seen in PD patients and can also present concomitant to RBD.[77] Its pathophysiology is unclear. Episodes with sleepwalking normally arise from non-REM sleep and can be distinguished from RBD episodes by a video-polysomnography. Coexistence of RBD and sleepwalking argue for a common pathophysiology of motor control during sleep.

Restless Legs Syndrome *(RLS) and Periodic Leg Movements During Sleep (PLMS)*

RLS is defined as an irresistible urge to move the legs, sometimes accompanied by uncomfortable, painful sensations. Typically, RLS symptoms emerge or become worse at rest, especially in bed at night, and are (partially) relieved by moving the legs or walking around. PLMS are periodic jerks of the lower extremity and can result in repeated awakenings and disruption of sleep. Restless legs syndrome (RLS) and periodic leg movements during sleep (PLMS) are seen as idiopathic entities, in the context of other sleep disorder, as well as in patients with PD. A recent study found a prevalence of 21.9% for RLS among 114 PD patients.[78]

The good clinical response to dopaminergic drugs and the association of PLMS with reduced striatal dopamine transporter binding suggests involvement of the dopaminergic system in PLMS.[79] The exact pathophysiology of PMLS and RLS in PD is still unclear. Disturbances in iron metabolism have been described for RLS. In RLS patients with a serum ferritin level below 50 pg/1, iron substitution can reduce RLS-related discomfort. Besides this, dopamine receptor agonists are the first line therapy for RLS; alternatively opioids and anticonvulsants can be used to treat RLS.

Lesions of the Arousal System in Parkinson's Disease

Altered sleep and vigilance are frequent symptoms in PD. As many as 60% of patients with PD experience insomnia, 15-59% show RBD, and 30% show excessive daytime sleepiness." While PD is undoubtedly a disorder with a pathology of dopamine neuronal loss, most arousal systems including noradrenergic neurons in the locus coeruleus, serotonergic neurons in the raphe, cholinergic neurons in the basal forebrain, and orexin/ hypocretin neurons in the hypothalamus, are affected by neuronal loss (Fig. 7-2). The loss of the neurotransmitter noradrenaline occurs consistently in PD and—according to Braak—earlier than in the dopaminergic neurons in the substantia nigra. This is thought to worsen with disease progression, either by increasing the vulnerability of dopamine-containing neurons or by reducing the recovery once they are damaged. There is 40-50% loss of noradrenergic neurons in the locus coeruleus and 20-40% loss of serotonergic neurons in the raphe median nucleus. In the basal forebrain, 32-93% of acetylcholine neurons are lost with disease progression.[81] However, loss of the dopaminergic neurons in the ventral periaqueducal gray region that contains "wake–active" dopaminergic neurons [82,83] is only 9% and histidine decarboxylase activity is reported to be normal in the brains of individuals with PD.84

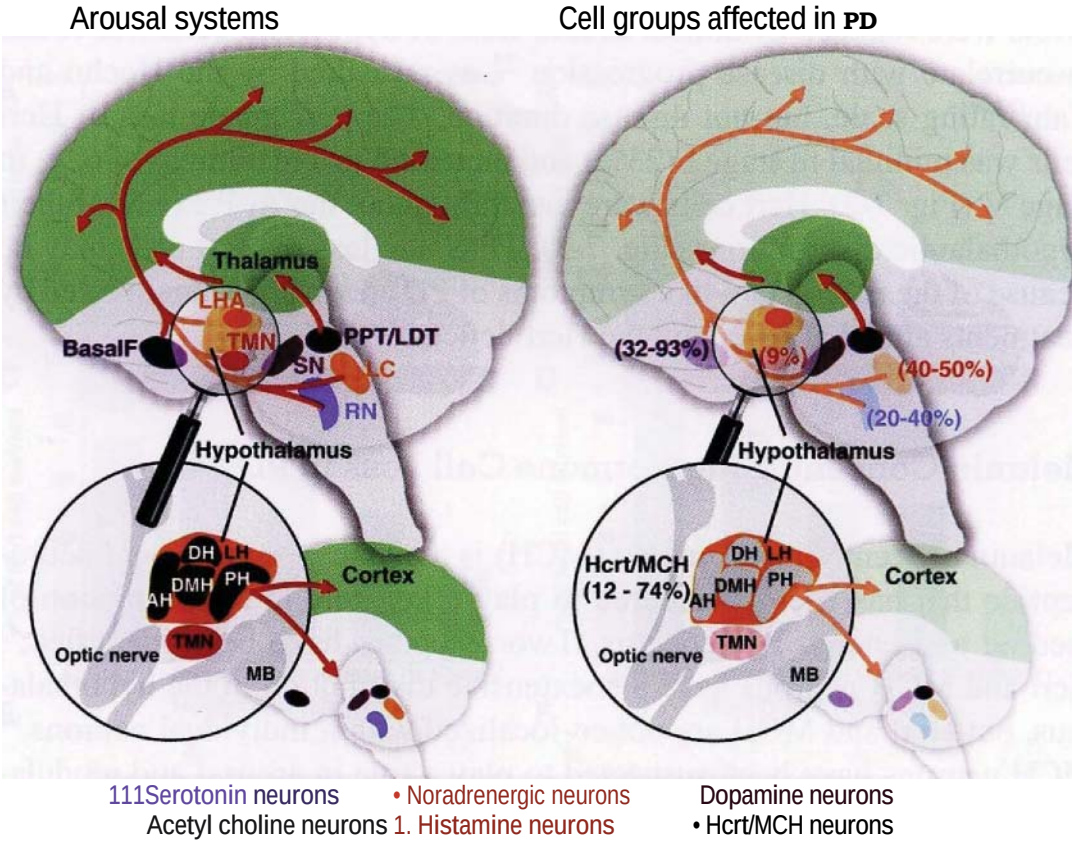

Figure 7-2. Pathology of the arousal system in Parkinson's disease. Left panel shows the cell groups involved in the arousal mechanism. The right panel shows the neuronal loss of the arousal system in PD. Arousal systems including noradrenergic neurons in the locus coeruleus; serotonergic neurons in the raphe; cholinergic neurons in the basal forebrain; Hcrt, MCH and histamine neurons in the hypothalamus are affected by neuronal loss.

Hypocretin/Orexin Cell Loss in Parkinson's Disease

The hypothalamic hypocretin (Hcrt or orexin) system plays a central role in the regulation of various functions, including sleep/wake regulation and metabolism. The two Hcrt peptides (Hcrt-1 and Hcrt-2), also known as orexins, are both encoded by the preprohypocretin gene, and the cell bodies are located in hypothalamus.[85,86] Two Hcrt receptors (Hcrtr-1 and Hcrtr-2) have been identified.[86] Hcrt fibers project widely throughout the brain, and generally have excitatory effects on their postsynaptic cells. Particularly notable are the projections of Hcrt cells to cholinergic and monoaminergic cells.' The similarity of the sleep disturbances of PD (discussed above) to narcolepsy suggest a common etiology. Narcolepsy is caused by loss of hypocretin-producing neurons, reflected in low cerebrospinal fluid (CSF) levels.[88-90]

Hcrt neurotransmission is affected in PD. Hcrt concentration in the pre-frontal cortex was almost 40% lower in PD patients, while ventricular CSF

levels were reduced by almost 25%.[24] Loss of hypocretin cells was found to correlate with disease progression [25] as measured by the Hoehn and Yahr rating scale, but not disease duration. The percentage loss of Hcrt cells was minimal in stage I (23%) and increased to a maximum of 62% in stage V (Fig. 7-3). Hcrt cells were lost throughout the A–P extent of their hypothalamic distributions (Fig. 7-3). Thus, the loss of Hcrt cells may be a cause of the narcolepsy-like symptoms of PD and may be ameliorated by treatments aimed at reversing the Hcrt deficit.[91•92]

Melanin Concentrating Hormone Cell Loss in PD

Melanin concentrating hormone (MCH) is a cyclic 19-amino-acid neuropeptide that has been considered to play a key role in the regulation of feeding and energy homeostasis. Two receptors have been identified.[93] Hcrt and MCH neurons have a coextensive distribution in the hypothalamus, but Hcrt and MCH are not co-localized within individual neurons." MCH neurons have been suspected to play a role in arousal and modulation of memory. Expression of c-fos in these cells is particularly strong after sleep rebound, consequent to sleep deprivation.[95] Intracerebroventricular injections of low doses of MCH induce an increase of REM sleep and with lesser amounts of slow wave sleep, suggesting that MCH plays a role in the homeostatic regulation of REM sleep.[96]

MCH neurons are more abundant in the human hypothalamus and have a wider rostrocaudal distribution than hypocretin neurons. MCH neurons are relatively more numerous in the posterior hypothalamus (Fig. 7-3). In PD, MCH cells are lost throughout the anterior to posterior extent of their hypothalamic distributions. The percentage loss of MCH cells is correlated with clinical stages of PD, as is the case with hypocretin neurons, with the smallest loss in stage I (12%) and the highest in stage V (74%). MCH cell loss was not correlated with disease duration. There was a significant increase in the size of neuromelanin containing cells in PD patients, but no difference in the size of surviving MCH or Hcrt cells relative to controls.[25]

The cause and pathophysiological mechanisms for Hcrt and MCH cell death are currently unknown. Whether Hcrt and MCH neurons show some neuropathological signs of dysfunction before loss remains to be determined. These issues need to be examined at the cellular and molecular level, but also in animal models. Dopamine replacement therapy has been the mainstay of antiparkinson treatment for the past three decades. Based on the new findings, detection of the loss of Hcrt and MCH cells and treatment of the deficits resulting from this loss may have a significant role in the diagnosis and treatment of Parkinson's disease.

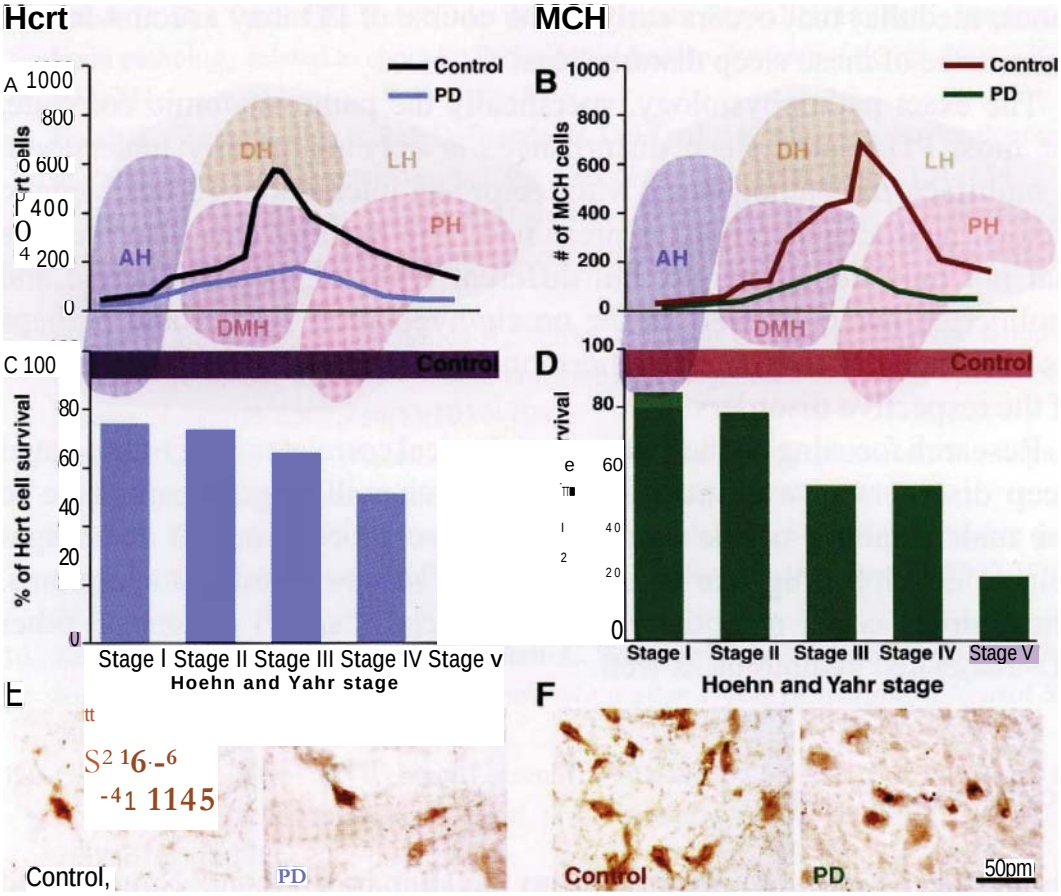

Figure 7-3. Hcrt and MCH pathology in Parkinson's disease. Hcrt cell loss (left panel) in different stages of PD (Hoehn and Yahr). The number of Hcrt cell was decreased with severity of the disease. The photomicrograph of Hcrt cells is from a control and a PD brain (stage V). Right panel shows MCH cell loss in different stages of PD. The number of MCH cells was decreased with severity of the disease. The photomicrograph of MCH cells is from a control and a PD brain (stage V). The loss of Hcrt and MCH cells was correlated with severity of the disease and not with duration. For cell count, a stereology program was used and for cell mapping a neurolucida program was used. The normal distribution of Hcrt and MCH cells in the hypothalamus is limited to AH, D1-1, DMH, LH and PH nulcei. AH=anterior hypothalamus, DH=dorsal hypothalamus, DMH=dorsomedial hypothalamus, LH-=lateral hypothalamus, PH=posterior hypothalamus. Bar=50iim.

Conclusions

In sum, sleep is frequently disturbed in PD patients. The spectrum of sleep-related disorders in PD patients comprises nocturnal troubles as well as symptoms that occur during daytime, like excessive daytime sleepiness and sleep attacks. Some of these disturbances (e.g. RBD and EDS) can emerge prior to the manifestation of PD-related motor symptoms and are potential markers that herald subsequent evolvement of PD. Patho-physiologically, degeneration of sleep-regulating centers in the brainstem

(pons, medulla) that occurs early in the course of PD may account for the occurrence of these sleep disturbances.

The exact pathophysiology, specifically the patho-anatomic correlate, for most PD-related sleep disturbances is only marginally understood_ A multifactorial pathogenesis with reciprocal interactions (drugs, genetic factors, neurodegeneration) is presumed. The existing data also indicate that not only dopaminergic, but different types of monoaminergic and cholinergic nuclei as well as the orexin/hypocretin system and perhaps also the melanin concentrating hormone are involved in the pathogenesis of the respective disorders.

Research focusing on the pathophysiological correlates ofPD-associated sleep disorders is warranted as this research will largely contribute to our understanding of the neurodegenerative process in PD and might help to develop drugs for the treatment of sleep-related PD symptoms. These drugs could potentially have beneficial ("side") effects on other PD-associated symptoms as well.

Acknowledgments

Tissue specimens were obtained from the Human Brain and Spinal Fluid Resource Center, West Los Angeles Healthcare Center, Los Angeles, CA. Supported by grants to JMS (NS14610, HL41370 and MH64109) and to YYL (NS42566) and the Medical Research Service of the Department of Veterans Affairs and by grants to WHO from the German Federal Ministry of Education and Research (funding code: 01GI0401) and the Willy and Monika Pitzer Foundation.

References

1. Porter B, Macfarlane R, Walker R. The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. *Eur J Neural.* 2008; 15(1):50-54.
2. Boddy F, Rowan EN, Lett D, O'Brien JT, McKeith IG, Bum DJ. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2007;22(6):529-535.
3. Dhawan V, Dhoat S, Williams NT, et al. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. *J Neural Sci.* 2006; 248(1-2):158-162.

4. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003;24(2): 197-211.
5. Braak *Ft,* Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res.* 2004;318(1):121-134.
6. Ghorayeb I, Loundou A, Auquier P, Dauvilliers Y, Bioulac B, Tison F. A nationwide survey of excessive daytime sleepiness in Parkinson's disease in France. *Mov Disord.* 2007;22(11):1567-1572.
7. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. *J Neurol.* 2007;254(8):1037-1043.
8. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology.* 2005;65(9):1442-1446.
9. Fabbrini G, Barbanti P, Aurilia C, Vanacore N, Pauletti C, Meco G. Excessive daytime sleepiness in de novo and treated Parkinson's disease. *Mov Disord.* 2002;17(5): 1026-1030.
10. Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Vanacore N, Meco G. Excessive daytime somnolence in Parkinson's disease. Follow-up after 1 year of treatment. *Neurol Sci.* 2003;24(3):178-179.
11. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: **is it** the drugs or the disease?. *Neurology.* 2006;67(5);853-858.
12. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology.* 2002;58(7): 1019-1024.
13. Oved D, Ziv I, Treves TA, Paleacu D, Melamed E, Djaldetti R. Effect of dopamine agonists on fatigue and somnolence in Parkinson's disease. *Mov Disord.* 2006;21(8): 1257-1261.
14. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord.* 2003;18(3):287-293.
15. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep.* 2002;25(8):905-909.
16. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neural Neurosurg Psychiatry.* 2005;76(12):1636-1639.
17. Rye DB, Johnston LH, Watts RL, Bliwise DL. Juvenile Parkinson's disease with REM sleep behavior disorder, sleepiness, and daytime REM onset. *Neurology.* 1999;53(8): 1868-1870.
18. Arnulf I, Bonnet AM, Damier P, et al. Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology.* 2000;55(2):281-288.
19. Baumann C, Ferini-Strambi L, Waldvogel D, Werth E, Bassetti CL. Parkinsonism with excessive daytime sleepiness-a narcolepsy-like disorder? *J Neurol.* 2005;252(2): 139-145.

20. Drouot X, Moutereau S, Nguyen JP, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. *Neurology.* 2003;61(4):540-543.
21. Maeda T, Nagata K, Kondo H, Kanbayashi T. Parkinson's disease comorbid with narcolepsy presenting low CSF hypocretin/orexin level. *Sleep Med.* 2006;7(8):662.
22. Overeem S, van Hilten JJ, Ripley B, Mignot E, Nishino S, Lammers GJ. Normal hypocretin-1 levels in Parkinson's disease patients with excessive daytime sleepiness. *Neurology.* 2002;58(3):498-499.
23. Yasui K, Inoue Y, Kanbayashi T, Nomura T, Kusumi M, Nakashima K. CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. *J Neurol Sci.* 2006;250(1-2):120-123.
24. Fronczek R, Overeem S, Lee SY, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain.* 2007;130(6):1577-1585.
25. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain.* 2007 ; 130(6):1586-1595.
26. Meindorfner C, KOrner Y, Moiler JC, Stiasny-Kolster K, Oertel WH, Kriiger HP. Driving in Parkinson's disease: mobility, accidents, and sudden onset of sleep at the wheel. *Mov Disord.* 2005 ;20(7): 832-842.
27. Frucht Si, Greene PE, Fahn S. Sleep episodes in Parkinson's disease: a wake-up call. *Mov Disord.* 2000;15(4):601-603.
28. MO1ler JC, Rethfeldt M, KOrner Y, et al. Daytime sleep latency in medication-matched Parkinsonian patients with and without sudden onset of sleep. *Mov Disord.* 2005;20(12):1620-1622.
29. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology.* 1999;52(9): 1908-1910.
30. Ferreira JJ, Thalamas C, Montastruc JL, Castro-Caldas A, Rascol 0. Levodopa monotherapy can induce "sleep attacks" in Parkinson's disease patients. *J Neurol.* 2001;248(5):426-427.
31. Bares M, Kanovsky P, Rektor I. Excessive daytime sleepiness and 'sleep attacks' induced by entacapone. *Fundam Clin Pharmacol.* 2003;17(1):113-116.
32. Santens P. Sleep attacks in Parkinson's disease induced by Entacapone, a COMT-inhibitor. *Fundam Clin Pharmacol.* 2003;17(1):121-123.
33. Tracik F, Ebersbach G. Sudden daytime sleep onset in Parkinson's disease: polysomnographic recordings. *Mov Disord.* 2001;16(3):500-506.
34. Homann CN, Homann B, Ott E, Park KB. Sleep attacks may not be a side effect of dopaminergic medication. *Mov Disord.* 2003;18(12):1569-1570; author reply 1571.
35. Paus S, Seeger G, Brecht HM, et al. Association study of dopamine D2, D3, D4 receptor and serotonin transporter gene polymorphisms with sleep attacks in Parkinson's disease. *Mov Disord.* 2004;19(6):705-707.
36. Rissling I, Geller F, Bandmann 0, et al. Dopamine receptor gene polymorphisms in Parkinson's disease patients reporting "sleep attacks". *Mav Disord.* 2004;19(11): 1279-1284.
37. Rissling I, Korner Y, Geller F, Stiasny-Kolster K, Ocrtel WH, Moller JC. Preprohypocretin polymorphisms in Parkinson disease patients reporting "sleep attacks". *Sleep.* 2005 ;28(7):871-875.

38. Pans S, Brecht HM, Koster J, Seeger G, Klockgether T, Wullner U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. *Mov Disord.* 2003;18(6): 659-667.
39. Korner Y, Meindorfner C, Moller JC, et al. Predictors of sudden onset of sleep in Parkinson's disease. *Mov Disord.* 2004;19(11):1298-1305.
40. Ferreira JJ, Desboeuf K, Galitzky M, et al. Sleep disruption, daytime somnolence and 'sleep attacks' in Parkinson's disease: a clinical survey in PD patients and age-matched healthy volunteers. *Eur J Neurol.* 2006; 13(3):209-214.
41. Diederich NJ, Vaillant M, Leischen M, et al. Sleep apnea syndrome in Parkinson's disease. A case-control study in 49 patients. *Mov Disord.* 2005;20(11):1413-1418.
42. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep.* 1986;9(2):293-308.
43. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology.* 1996;46(2):388-393.
44. Gagnon JF, Bedard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology.* 2002;59(4):585-589.
45. Pacchetti C, Manni R, Zangaglia R, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. *Mov Disord.* 2005;20(11):1439-1448.
46. Olson EJ, Boeve **BF, Silber MI-1**. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain.* 2000;123(2): 331-339.
47. de Maindreville AD, Fenclon G, Mahieux F. Hallucinations in Parkinson's disease: a follow-up study. *Mov Disord.* 2005;20(2):212-217.
48. Onofrj M, Thomas A, D'Andreamatteo G, et al. Incidence of RBD and hallucination in patients affected by Parkinson's disease: 8-year follow-up. *Neurol Sci.* 2002; 23 Suppl 2: 591-4.
49. Uchiyama M, Isse K, Tanaka K, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology.* 1995;45(4):709-712.
50. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. *Brain.* 2000;123(6):1155-1160.
51. Stiasny-Kolster K, Doerr Y, Moller JC, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. *Brain.* 2005; 128(1):126-137.
52. Kunz D, Bes F. Melatonin effects in a patient with severe REM sleep behavior disorder: case report and theoretical considerations. *Neuropsychohiology.* 1997;36(4): 211-214.
53. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov Disord.* 1999;14(3):507-511.
54. Takeuchi N, Uchimura N, Hashizume Y, et al. Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci.* 2001;55(3):267-269.

55. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med.* 2003;4(4): 281-284.
56. Medeiros CA, Carvalhedo de Bruin PF, Lopes LA, Magalhaes MC, de Lourdes Seabra M, de Bruin VM. Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease. A randomized, double blind, placebo-controlled study. *J Neurol;254(4):459-464.*
57. Paus S, Schmitz-Hubsch T, Wuliner U, Vogel A, Klockgether T, Abele M. Bright light therapy in Parkinson's disease: a pilot study. *Mov Disord.* 2007;22(10):1495-1498.
58. Willis GL, Turner EJ. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. *Chronobiol Int.* 2007;24(3):521-537.
59. Tan A, Salgado M, Fahn S. Rapid eye movement sleep behavior disorder preceding-Parkinson's disease with therapeutic response to levodopa. *Ma[y] Disord.* 1996;11(2): 214-216.
60. Ozekmekci S, Apaydin H, Kilic E. Clinical features of 35 patients with Parkinson's disease displaying REM behavior disorder. *Clin Neurol Neurosurg.* 2005;107(4): 306-309.
61. Schmidt MH, Koshal VB, Schmidt HS. Use of pramipexole in REM sleep behavior disorder: results from a case series. *Sleep Med.* 2006;7(5):418-423.
62. Fantini ML, Gagnon JF, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. *Neurology.* 2003 ;61 (10): 1418-1420.
63. Massironi G, Galluzzi S, Frisoni GB. Drug treatment of REM sleep behavior disorders in dementia with Lewy bodies. *Int Psychogeriatr.* 2003;15(4):377-383.
64. Hendricks JC, Morrison AR, Mann GL. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. *Brain Res.* 1982;239(1):81-105.
65. Lai YY, Hsieh KC, Nguyen D, Peever J, Siegel J M. Neurotoxic lesions at the ventral mesopontine junction change sleep time and muscle activity during sleep: An animal model of motor disorders in sleep. *Neuroscience.* 2008;154(2):431-443.
66. Lai YY, Siegel .IM. Physiological and anatomical link between Parkinson-like disease and REM sleep behavior disorder. *Mol Neurobiol.* 2003;27(24):137-152.
67. Morrison AR. Paradoxical sleep without atonia. *Arch Ital Biol.* 1988;126(4): 275-289.
68. Plazzi G, Montagna P. Remitting REM sleep behavior disorder as the initial sign of multiple sclerosis. *Sleep Med.* 2002;3(5):437-439.
69. Xi Z, Luning W. REM sleep behavior disorder in a patient with pontine stroke. *Sleep Med.* 2009;10(1):143-146.
70. Kimura K, Tachibana N, Kohyama J, Otsuka Y, Fukazawa S, Waki R. A discrete pontine ischemic lesion could cause REM sleep behavior disorder. *Neurology.* 2000;55(6): 894-895.
71. Mazza S, Soucy J, Gravel P, et al. Assessing whole brain perfusion changes in patients with REM sleep behavior disorder. *Neurology.* 2006;67(9):1618-1622.
72. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pcdunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. *Proc Natl Acad Sci. USA.* 1987;84(16):5976-5980.

73. Turner RS, D'Amato CJ, Chervin RD, Blaivas M. The pathology of REM sleep behavior disorder with comorbid Lewy body dementia. *Neurology.* 2000;55(11):1730-1732.
74. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain.* 2007;130(11):2770-2788.
75. Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. *Nature.* 2006;441(7093):589-94.
76. Siegel,J.M. *REM sleep in Principles and Practice of Sleep Medicine* (eds. Kryger, M.H., Roth, T. & Dement, W.C. (Elsevier Saunders, Philadelphia). 2005;120-135.
77. Poryazova R, Waldvogel D, Bassetti CL. Sleepwalking in patients with Parkinson disease. *Arch Neurol.* 2007;64(10): 1524-1527.
78. Gomez-Esteban JC, Zarranz JJ, Tijero B, et al. Restless legs syndrome in Parkinson's disease. *Mov Disord.* 2007;22(13):1912-1916.
79. Happe S, Pirker W, Klosch G, Sauter C, Zeitlhofer J. Periodic leg movements in patients with Parkinson's disease are associated with reduced striatal dopamine transporter binding. *J Neurol.* 2003;250(1):83-86.
80. De Cock VC, Vidailhet M, Arnulf I. Sleep disturbances in patients with parkinsonism. Nat. *Clin Pract Neurol.* 2008;4(5):254-66.
81. Jellinger KA. The pathology of Parkinson's disease. *Adv Neurol.* 2001;86:55-72.
82. Lu J, Jhou TC, Saper CD. Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. *J Neurosci.* 2006;26(1):193-202.
83. Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain.* 1999; 122(8):1437-48.
84. Garbarg M, Javoy-Agid F, Schwartz JC, Agid Y. Brain histidine decarboxylase activity in Parkinson's disease. *Lancet.* 1983;1(8314-5):74-75.
85. de Lecea L, Kilduff TS, Peyron C, ct al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA.* 1998;95(1):322-327.
86. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell.* 1998;92(4):573-85.
87. Siegel JM. Hypocretin (orexin): role in normal behavior and neuropathology. *Annu Rev Psychol.* 2004;55:125-48.
88. Peyron C, Faraco .1, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med.* 2000;6(9):991-997.
89. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons **in** human narcolepsy. *Neuron.* 2000; 27(3):469-474.
90. Thannickal TC, Siegel JM, Nienhuis R, Moore RY. Pattern of hypocretin (orexin) soma and axon loss, and gliosis, in human narcolepsy. *Brain Pathol.* 2003;13(3):340-351.
91. Deadwyler SA, Porrino L, Siegel JM, Hampson RE. Systemic and nasal delivery of orexin-A (hypocretin-1) reduces the effects of sleep deprivation on cognitive performance in nonhuman primates. *Journal of Neuroscience.* 2007;27(52):14239-14247.
92. John J, Wu MF, Siegel JM. Systemic administration of hypocretin-1 reduces cataplexy and normalizes sleep and waking durations in narcoleptic dogs. *Sleep Res. Online.* 2000;3(1):23-28.

93. Shimazaki T, Yoshimizu T, Chaki S. Melanin-concentrating hormone MCH1 receptor antagonists: a potential new approach to the treatment of depression and anxiety disorders. *CNS Drugs.* 2006;20(10): 801-811.
94. Broberger C, De Lecea L, Sutcliffe JG, Wokfelt T. Hypocretin/orexin- and melanin-concentrating hormone-expressing cells form distinct populations in the rodent lateral hypothalamus: relationship to the neuropeptide Y and agouti gene-related protein systems. *J Comp Neurol.* 1998;402(4): 60-74.
95. Modirrousta M, Mainville L, Jones BE. Orexin and MCH neurons express c-Fos differently after sleep deprivation vs. recovery and bear different adrenergic receptors. *Eur J Neurosci.* 2005;21(10):2807-2816.
96. Verret L, Goutagny R, Fort P, et al. A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. *BMC Neurosci.* 2003; 9:4:19.