

Therapeutic potential of melatonin and its analogs in Parkinson's disease: focus on sleep and neuroprotection

Venkatramanujam Srinivasan, Daniel P. Cardinali, Uddanapalli S. Srinivasan, Charanjit Kaur, Gregory M. Brown, D. Warren Spence, Rüdiger Hardeland and Seithikurippu R. Pandi-Perumal

Abstract: Sleep disorders constitute major nonmotor features of Parkinson's disease (PD) that have a substantial effect on patients' quality of life and can be related to the progression of the neurodegenerative disease. They can also serve as preclinical markers for PD, as it is the case for rapid eye movement (REM)-associated sleep behavior disorder (RBD). Although the etiology of sleep disorders in PD remains undefined, the assessment of the components of the circadian system, including melatonin secretion, could give therapeutically valuable insight on their pathophysiology. Melatonin is a regulator of the sleep/wake cycle and also acts as an effective antioxidant and mitochondrial function protector. A reduction in the expression of melatonin MT₁ and MT₂ receptors has been documented in the substantia nigra of PD patients. The efficacy of melatonin for preventing neuronal cell death and for ameliorating PD symptoms has been demonstrated in animal models of PD employing neurotoxins. A small number of controlled trials indicate that melatonin is useful in treating disturbed sleep in PD, in particular RBD. Whether melatonin and the recently developed melatonergic agents (ramelteon, tasimelteon, agomelatine) have therapeutic potential in PD is also discussed.

Keywords: agomelatine, insomnia, light therapy, melatonin, oxidative stress, Parkinson's disease, ramelteon, REM sleep behavior disorder, tasimelteon

Introduction

Parkinson's disease (PD) affects several million people worldwide, irrespective of gender, social, ethnic, economic, or geographic boundaries [Elbaz and Moisan, 2008]. Key symptoms, such as tremor, rigidity, bradykinesia and postural instability, develop when about three quarters of dopaminergic cells are lost in the substantia nigra pars compacta, and consequently the smooth, coordinated regulation of striatal motor circuits is hampered [Maguire-Zeiss and Federoff, 2010; Tansey *et al.* 2007; Zhang *et al.* 1999]. Other nonmotor symptoms are seen in PD, and some of them, such as hypsomia, depression, or rapid eye movement (REM)-associated sleep behavior disorder (RBD), can precede the onset of disease. Nonmotor symptoms are often misdiagnosed and untreated although their appearance is indicative of a worse prognosis and lower quality of life.

At this time, there is no treatment that will delay or stop the progression of PD, and medications

currently available are mostly symptomatic. Although the increasing incidence of age-associated neurodegenerative diseases such as PD has been attributed to the augmented generation of free radicals and the associated oxidative stress, which is enhanced in certain regions of the aging brain [Gibson *et al.* 2010; Fahn and Cohen, 1992; Olanow, 1992], antioxidants, such as vitamin E that attenuates 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) Parkinsonism in rodents [Itoh *et al.* 2006], have not had significant effects on the evolution of the disease in humans [The Parkinson Study Group, 1993].

A number of studies have repeatedly documented the prevalence of sleep disturbances in PD, which in some cases was close to 90% [Comella, 2007, 2006; Garcia-Borreguero *et al.* 2003; Happe *et al.* 2002; Trenkwalder, 1998; Lees *et al.* 1988]. In the present manuscript attention is focused on the possible role of sleep disturbance and disruption of circadian rhythm function in the

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Correspondence to:
Daniel P. Cardinali,
MD, PhD

Director, Departamento de
Docencia e Investigación,
Facultad de Ciencias
Médicas, Pontificia
Universidad Católica
Argentina, Av. Alicia
Moreau de Justo 1500, 4°
piso, 1107 Buenos Aires,
Argentina
danielcardinali@uca.edu.ar
and
danielcardinali@fibertel.com.ar

**Venkatramanujam
Srinivasan**

Sri Sathya Sai Medical
Educational and Research
Foundation, Prasanthi
Nilayam, Plot-40, Kovai
Thirunagar, Coimbatore
641014, India

Uddanapalli S. Srinivasan
Department of
Neurosciences, MIOT
Hospital, Manapakkam,
Chennai 600089, India

Charanjit Kaur
Department of Anatomy,
Yong Loo Lin School of
Medicine, National
University of Singapore,
Singapore 117597,
Singapore

Gregory M. Brown
Department of Psychiatry,
Faculty of Medicine,
University of Toronto,
Centre of Addiction and
Mental Health, 250
College Street, Toronto,
ON, Canada M5T 1R8

D. Warren Spence
323 Brock Avenue,
Toronto, ON, Canada
M6K 2M6

Rüdiger Hardeland
Johann Friedrich
Blumenbach Institute of
Zoology and Anthropology,
University of Goettingen,
Berliner St 28, Lower
Saxony, D-37073
Goettingen, Germany

**Seithikurippu
R. Pandi-Perumal**
Somnogen Inc, College
Street, Toronto, ON,
Canada M6H 1C5

progression of PD. More particularly, the activity of melatonin, whose secretion is a key signal for sleep/wake cycle organization and has a relevant neuroprotective activity in a number of experimental models, is discussed. It has been shown that a decrease in melatonergic receptors occurs in the amygdala and the substantia nigra of PD patients [Adi *et al.* 2010] and that this reduction coexists with PD-associated sleep disturbances. Further, there is some clinical evidence that melatonin can be a useful add-on therapy for RBD in PD [Aurora *et al.* 2010].

With the introduction of new melatonergic agents such as ramelteon, tasimelteon, and agomelatine, the opportunity now exists for designing clinical trials to determine whether these agents have merit for treating sleep disorders in PD. Inasmuch as melatonin has been demonstrated to be an effective sleep regulator and multifunctional antioxidant, any possible consideration of its role in the etiology of PD could be relevant not only for providing new insights of the disease, but also for giving background to the therapeutic use of melatonergic agonists in PD.

Basic sleep physiology

The sleep-switch model (Figure 1), originally proposed by Saper and colleagues, describes flip–flop mutual inhibitions among sleep-associated activities in the ventrolateral preoptic nucleus and wakefulness associated activities in the tuberomammillary nucleus, dorsal raphe nucleus and locus coeruleus (LC) [Saper *et al.* 2005]. The components of the ascending reticular activating system also include dopamine (DA)-containing neurons in the substantia nigra pars compacta (SN) and the ventral tegmental area (A10 area), the basal forebrain (cholinergic neurons) and the pedunculopontine and laterodorsal tegmenti (PPT/LDT) (cholinergic neurons). Orexin–melanocyte concentrating hormone neurons in the lateral hypothalamus provide stimulatory input to the wakefulness-promoting areas (Figure 1).

The daily sleep/wake cycle is influenced by two separate processes: (1) the endogenous biological clock that drives the circadian rhythm of sleep/wake cycle (Process C, for ‘circadian’) and (2) a homeostatic component (Process S, for ‘sleep’) that influences sleep propensity, a state which is determined by the immediate history of sleep and wakefulness and additionally by the duration of

previous sleep episodes [Borbely, 1982]. These two processes, which interact continuously, determine the consolidated bout of sleep at night and the consolidated bout of wakefulness during daytime.

A ‘forced desynchrony paradigm’ (in which the subject’s circadian rhythms are experimentally desynchronized) has been used to study the contribution of each of these components. Observations of subjects whose circadian rhythms had been experimentally desynchronized have supported the inference that REM sleep is driven by the circadian component whereas slow-wave sleep (SWS) (or non-REM sleep) is driven by the homeostatic component [Scheer *et al.* 2007].

The circadian system is also known as a wake-promoting system because it determines the strength of wakefulness [Borbely, 1982]. The circadian rhythm in the secretion of the pineal hormone melatonin has been shown to be responsible for the sleep rhythm in both normal and blind subjects (i.e. in the absence of the synchronizing effect of light). It is possible that melatonin feedbacks at the suprachiasmatic nucleus (SCN) to inhibit the circadian signal responsible for promoting wakefulness [Wehr *et al.* 2001; Dijk *et al.* 1997; Sack *et al.* 1992] (Figure 1).

Since the SCN interacts with both sleep regulatory mechanisms, Process S and Process C, it was suggested that a functional disruption of the SCN is involved in disorders of sleep and wakefulness [Saper *et al.* 2005]. The role of the SCN in sleep regulation was first studied in the squirrel monkey. In this primate species lesions made in the SCN caused either loss of sleep or prolonged sleep [Edgar *et al.* 1993]. It is suggested that circadian signals emanating from the SCN promote wakefulness during the day and may facilitate sleep during the subjective night. It is interesting to note that the neural pathways from the SCN that promote wakefulness are complemented by those that are involved in the promotion of sleep (Figure 1) [Saper *et al.* 2005].

Pathophysiology of sleep disorders in Parkinson’s disease

Several studies have revealed that Lewy’s body pathology, a characteristic feature of cellular PD lesions, is pronounced not only in SN but also in other central nervous system (CNS) regions such as the lower brainstem and several nuclei of the autonomic nervous system [Beach *et al.* 2009;

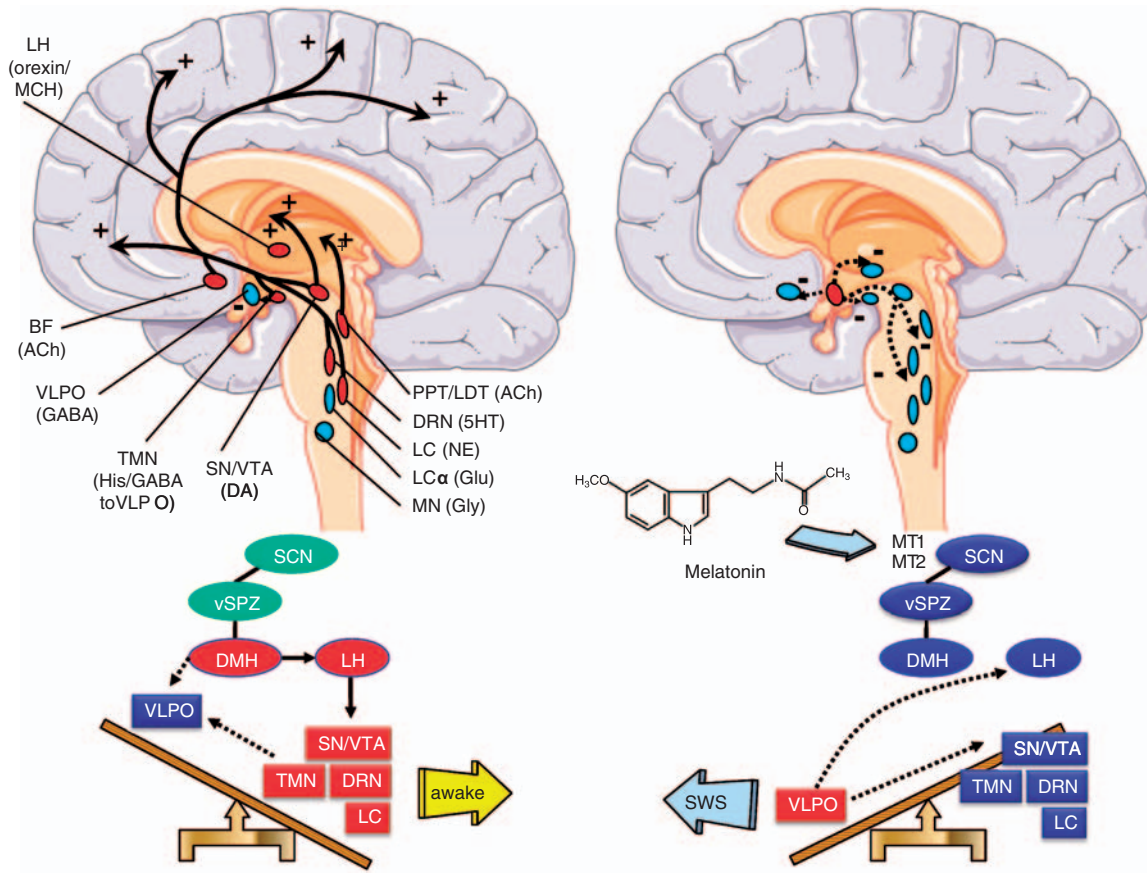


Figure 1. *Upper part:* Schematic representation (modified from Saper *et al.* [2005]) of key components of the 'ascending reticular arousal system' mediating wakefulness (left) and the inhibitory control on these components during slow-wave sleep (SWS) by GABAergic neurons of the ventrolateral preoptic nucleus (VLPO), located at the bottom of the anterior hypothalamus (right). During wakefulness the histaminergic neurons in the ventral tuberomammillary nucleus (TMN) at the bottom of the posterior hypothalamus provide a strong inhibitory influence to the VLPO. The components of the ascending reticular activating system further include the dorsal raphe nuclei (DRN, 5HT neurons), the locus coeruleus (LC, noradrenergic neurons), the pedunculo-pontine and laterodorsal tegmenti [PPT/LDT, acetylcholine (ACh)-containing neurons], DA-containing neurons in the substantia nigra (SN) and the ventral tegmental area (VTA), and the basal forebrain (BF, cholinergic neurons). Orexin–melanocyte concentrating hormone (MCH) neurons on the lateral hypothalamus (LH) provide stimulatory input to the wakefulness-promoting areas. The LC- α and magnocellular nuclei (MN), participating in REM-induced atonia (see Figure 2) are also depicted. Red labels denote activation, while blue labels denote inhibition. In PD several of these monoaminergic areas promoting wakefulness degenerate (see the text) which is a feasible explanation for the increased somnolence found. *Lower part:* the SCN, projecting through the hypothalamic ventral subparaventricular zone (sPVZ), promotes wakefulness principally by augmenting the activity of orexinergic/MCH-containing neurons in LH. Melatonin inhibits via MT₁ and MT₂ receptors, SCN activity and promotes sleep. In PD a decrease of MT₁ and MT₂ receptors are found in SN and amygdala [Adi *et al.* 2010], which could explain the impoverishing of sleep.

Braak *et al.* 2007, 2003]. According to Braak and colleagues, the first stage of PD involves deposition of α -synuclein in the anterior olfactory nucleus, the olfactory bulb, and the dorsal motor nucleus of the vagus [Braak *et al.* 2007, 2003]. In addition, neurons of the unmyelinated lamina-1 spinal cord and peripheral autonomic ganglia are also affected. Stage 2 is characterized

by neurodegenerative processes comprising brainstem cholinergic, serotonergic, and noradrenergic regions, such as the PPT/LDT, LC and the and reticular-activating system, the dopaminergic neurons of the SN being affected only at stage 3. At more advanced stages (4–6) cortical neurons become affected [Beach *et al.* 2009; Braak *et al.* 2007, 2003].

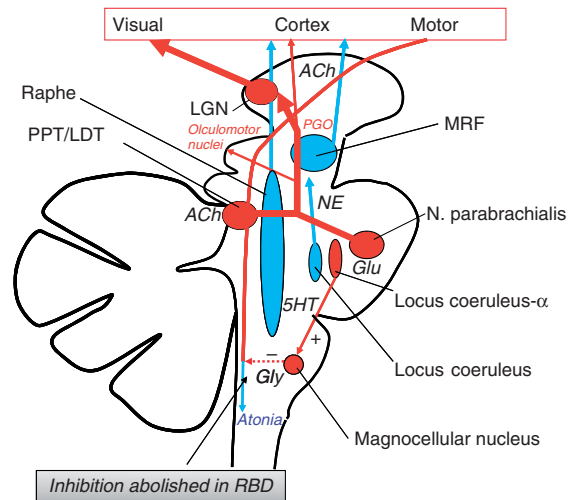


Figure 2. A schematic drawing of nuclei and neural structures involved in the regulation of REM sleep. Pontogeniculoccipital (PGO) activity is typical of REM sleep and can be recorded in animals with the pons isolated from the rest of the brain. The PGO system can be activated by drugs or lesions that lead to a suppression of 5HT secretion in the Raphe nuclei. PGO generators use acetylcholine (ACh) as a transmitter. During REM, the increasing loss of activity in the locus coeruleus leads to disinhibition of locus coeruleus- α which in turn activates the magnocellular nucleus via glutamatergic (Glu) projections. Glycine (Gly)-mediated inhibition of motor neurons in spinal cord is activated and atonia ensues. The Locus coeruleus- α begins to be active, a few minutes before the actual onset of REM. In PD, loss of REM sleep atonia and/or increased locomotor drive have been suggested as likely mechanisms for the clinical expression of REM-associated sleep behavior disorder (RBD) [Boeve *et al.* 2007b]. LGN: lateral geniculate nucleus. PPT/LDT: pedunculopontine and laterodorsal tegmenti.

Despite some debates on the preclinical processes [Wu *et al.* 2011], there can be no doubt about a remarkably extended period of neurological changes prior to the appearance of classic PD symptoms. In several cases, these changes have been assumed to date back to the perinatal period [Wu *et al.* 2011].

This particular pattern of neurodegeneration explains why sleep disorders have such a high prevalence rate in PD and why they deserve consideration for clinical prediction of the disease [Postuma *et al.* 2010]. Indeed, neurological non-motor and psychiatric manifestations of PD often precede the traditionally recognized motor manifestations [Postuma *et al.* 2010;

Savica *et al.* 2010]. Case-control and cohort studies suggest that depression and anxiety disorders are also one of the earliest manifestations of PD [Postuma *et al.* 2010; Weisskopf *et al.* 2003; Shiba *et al.* 2000]. Since sleep disturbances in PD patients are associated with cognitive decline and psychiatric symptoms [Comella, 2007, 2006], it has been suggested that attention be focused on the development of targeted interventions for early correction of nonmotor disorders [Naismith *et al.* 2010].

Sleep and chronobiological disorders in PD

Most patients with PD experience sleep-related symptoms, such as difficulty in initiating and maintaining sleep, excessive daytime somnolence (EDS), and parasomnias such as RBD [Ceravolo *et al.* 2010]. When occurring in the absence of medication these PD sleep disorders are classified as primary and are regarded as intrinsic to PD, while those appearing subsequent to medications are classified as secondary [Friedman and Chou, 2004].

The most common sleep-related manifestation of PD is sleep fragmentation, with a prevalence of 39% [Tandberg *et al.* 1999], concomitant with PD motor disorders [Larsen, 2003] or nocturia [Lees *et al.* 1988]. Nocturnal motor activity, including off-state dystonia, cramps, tremor or severe akinesia, and rigidity tend to produce painful postures or problems in turning in bed [Chaudhuri *et al.* 2006; Dhawan *et al.* 2006b].

Overall, difficulties in falling asleep or in maintaining restorative sleep are found in PD. Disorders of sleep initiation and maintenance are characterized by either a reduction in the stages 3/4 of non-REM sleep or by a decrease in REM sleep [Adler, 2005; Adler and Thorpy, 2005]. They may represent a direct effect of disease on sleep architecture or could be an indirect effect mediated by either the cardinal parkinsonian symptoms or by the medication employed [Suzuki *et al.* 2007; Kaynak *et al.* 2005; Garcia-Borreguero *et al.* 2003; Young *et al.* 2002].

Restless legs syndrome is also prevalent in PD patients and has been considered the consequence of local iron deficiency in the SN, although evidence in this respect is not compelling [Nomura *et al.* 2006; Ondo *et al.* 2002]. About 20% of PD patients exhibit either of obstructive or central type sleep apnea [Arnulf *et al.* 2002].

EDS [Comella, 2006; Garcia-Borreguero *et al.* 2003], ultimately affecting health-related quality of life [Weintraub *et al.* 2004; Scaravilli *et al.* 2003], affects up to 50% of PD patients [Monderer and Thorpy, 2009; Comella, 2006; Hobson *et al.* 2002]. Factors that contribute to EDS in PD include PD motor disability, impact of PD and other medications on alertness, presence of depression and dementia, and concurrent medical illnesses [Simuni, 2004]. The severity of EDS does not correlate with the degree of nocturnal sleep impairment in PD [Arnulf *et al.* 2002] and increases with the progression of the disease. Although it has been suggested that intake of both dopaminergic agonists and levodopa are contributing factors in the development of EDS [Mehta *et al.* 2008], it could also be due to the underlying pathology of PD [Erro *et al.* 2010; Arnulf *et al.* 2002]. In a study performed in one of our laboratories, day-to-day sleep quality self-evaluations by sleep log and actigraphy, PD sleep scale (PDSS), daytime somnolence and sleep log daily wellbeing could differentiate PD patients from healthy controls, but only daily wellbeing segregated moderately/severely affected PD patients from the less affected patients [Pérez Lloret *et al.* 2009]. Nocturnal activity, as assessed by actigraphy, increased only in PD patients taking higher doses of levodopa, independently of their disease's severity. Multivariate regression analysis showed that PD severity and depression were the only predictors of reduced sleep quality [Pérez Lloret *et al.* 2009].

Neuropsychiatric symptoms, such as vivid dreams, nightmares and nocturnal hallucinations, or RBD, are commonly observed in PD [Chaudhuri *et al.* 2006, 2002; Dhawan *et al.* 2006a, 2006b; Grandas and Iranzo, 2004]. RBD in PD may occur as a prodromal feature, predating motor symptoms by several years [Postuma *et al.* 2010]. Its prevalence, which is thought to be 60%, has been identified in longitudinal studies and is suspected to be a predictor for dementia in longitudinal studies [Marion *et al.* 2008; Vendette *et al.* 2007]. RBD is characterized by a loss of skeletal muscle atonia with prominent motor activity and dreaming [Boeve *et al.* 2007a; Olson *et al.* 2000] (Figure 2).

Numerous cases of RBD have been found in clinically diagnosed PD patients [Boeve *et al.* 2007a; Schenck *et al.* 1996]. In several studies RBD has

been demonstrated to be more frequent in the male than female gender, but the reasons for this male predominance are not yet known [Ceravolo *et al.* 2010]. Loss of REM sleep atonia and/or increased locomotor drive have been suggested as likely mechanisms for the clinical expression of human RBD [Boeve *et al.* 2007b] (Figure 2). There is a tendency for the dream content to involve an aggressive, attacking, or chasing theme. Nightmare behaviors such as screaming, kicking, punching, and injuring the bed partner are quite common [Jahan *et al.* 2009].

Nocturnal disturbance and sleep arousals as measured by actigraphy are specific to RBD seen in PD [Naismith *et al.* 2010]. A loss of orexin neurons and of cells secreting melanin-concentrating hormone in the hypothalamus of PD patients is said to be responsible for nocturnal insomnia, RBD and hallucinations [Thannickal *et al.* 2008, 2007]. However, changes in orexin do not necessarily underpin associated RBD sleep disturbances [Compta *et al.* 2009]. The investigation of the components of the circadian system (that mediates the onset and timing of REM sleep), including the pattern and timing of melatonin secretion, combined with clinicopathological assessments, could be useful for defining the chronobiological correlates of RBD in PD.

Imaging studies have been useful in identifying the role of dopaminergic alterations in the pathogenesis of PD sleep disorders [Mehta *et al.* 2008]. In a study conducted on 10 PD patients, polysomnographic (PSG) parameters were compared with dopaminergic functions in the striatum and upper brainstem using [¹⁸F] fluoro-DOPA (F-DOPA) positron emission tomography. Decreased F-DOPA uptake was found to correlate with increased REM sleep duration in early PD [Hilker *et al.* 2003]. Treatment of PD with dopaminergic drugs has been shown to promote sleep when given in low doses, but when administered in higher doses it prolonged sleep latency and caused fragmentation of sleep [van Hilten *et al.* 1994]. Selegiline, when given to PD patients, caused alerting effects and caused difficulty in falling asleep [Lavie *et al.* 1980]. PD patients when given pergolide as an add-on drug increased nocturnal activity and worsened sleep fragmentation as compared with placebo [Comella, 2006].

Thus, both dopaminergic drugs as well as non-dopaminergic drugs commonly used for treatment of PD may affect sleep and degrade the quality of life in these patients. Hence, there is a necessity to introduce clinically effective non-toxic sleep-promoting drugs for treatment of sleep disorders seen in PD. In this context the neurohormone melatonin and particularly its agonists ramelteon, tasimelteon, and agomelatine offer promising features for the treatment of sleep disorders associated with PD.

In the last decade many studies of molecular clock mechanisms involved in regulating the circadian physiology and behavior in mammals have been carried out. These have focused on central circadian pacemaker, the SCN of the anterior hypothalamus, as well as on a number of peripheral tissues and cells [Dibner *et al.* 2010; Liu *et al.* 2007]. Several circadian genes, known as ‘clock genes’, have been identified. Among these *Per1* and *Bmal1* are regarded as the best markers of the molecular clock. Disruptions of *Bmal1* and *Per1* expression in mice brought about altered circadian behavior and dysregulation of circadian patterns in cell function [Kondratov *et al.* 2006; Cermakian *et al.* 2001]. The circadian clock genes *Per1* and *Bmal1*, which are expressed in many peripheral cells, are also located in leukocytes of healthy humans [Fukuya *et al.* 2007], and studies of these genes have been undertaken in total leukocytes of PD patients [Cai *et al.* 2010b]. During the dark phase expression of *Bmal1* but not of *Per1* was much reduced in PD patients, suggesting an alteration of the peripheral molecular clockwork in Parkinsonism. The decrease in expression of *Bmal1* in PD patients correlated with the United Parkinson’s Disease Rating Scale score and Pittsburgh Sleep Quality Index score [Cai *et al.* 2010b].

Alteration of clock gene expression could be the basis for many of the circadian rhythm disturbances that are commonly seen in PD. However, it must be noted that the discussion of circadian aspects of PD in a clinically meaningful context is an exceedingly complex problem due to the numerous confounding factors, such as pain, bladder dysfunction, sedation from medications, depression, anxiety, daytime naps, etc. Therefore, caution is needed in interpreting clinical data.

Parkinsonian symptoms themselves undergo circadian fluctuations [Willis, 2008]. Patients with

PD often experience worsening of symptoms in the afternoon and the evening. Patients with PD also experience time-dependent responsiveness to dopaminergic stimulation [Bruguerolle and Simon, 2002]. In PD patients Fertl and coworkers reported that levodopa-treated patients but not the ‘*de novo*’ patients showed a phase advance of the melatonin circadian rhythm [Fertl *et al.* 1993, 1991]. Bordet and colleagues confirmed those results and showed no changes in locomotor activity, cortisol nor temperature rhythms in ‘*de novo*’ PD patients [Bordet *et al.* 2003]. In this study a decrease in amplitude of circulating melatonin rhythm was also observed.

Corresponding data were obtained in a recent study performed in one of our laboratories in which untreated (‘*de novo*’), levodopa-treated without motor fluctuations (stable) and levodopa-treated fluctuating idiopathic PD patients were examined in their sleep/wake rhythmicity [Pérez Lloret *et al.* 2010]: treated patients of stable and fluctuating groups showed significantly earlier waking and ending of the immobility time. Indeed, sleep/wake rhythm alterations in PD patients are expressed along a continuum, varying as a function of levodopa-treatment intensity.

A primary approach to the treatment of sleep disorders in PD concerns to sleep hygiene, since so far there are no controlled data on any specific hypnotic agent in PD. Since previous sleep hygiene measures are often not sufficient, it is recommended that hypnotic agents must be prescribed with caution with close monitoring for potential side effects, specifically confusion and daytime sleepiness [Ceravolo *et al.* 2010]. This relative lack of safe pharmacological tools to treat PD sleep disorders has focused interest on recently developed pharmacological agents such as ramelteon, agomelatine, and tasimelteon that are melatonin receptor agonists which, compared with melatonin itself, have a longer half life and greater affinity for melatonin receptors. Consequently, they are thought to hold promise for treating a variety of sleep disorders.

One important point when dealing with the effect of melatonin analogs is to understand that they are not regular hypnotic drugs resembling benzodiazepines and their derivatives. Melatonin-like compounds exert a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep

inducing effect, quite mild as compared with the efficacy of benzodiazepines.

Melatonin: physiological role

Melatonin, which occurs ubiquitously in nature, is a remarkable molecule with diverse physiological functions [Hardeland *et al.* 2011; Reiter *et al.* 2010; Pandi-Perumal *et al.* 2006b]. In mammals circulating melatonin is synthesized by the pineal gland with a nocturnal maximum of about 200 pg/ml and a daytime nadir of less than 10 pg/ml [Arendt and Skene, 2005]. Although synthesis also occurs in various other regions of the body such as the gastrointestinal tract, skin, lymphocytes, platelets, bone marrow cells, retina, or thymus [Hardeland *et al.* 2011; Reiter *et al.* 2010; Pandi-Perumal *et al.* 2006b], in all of these tissues melatonin has either an autocrine or a paracrine role.

Once formed melatonin is not stored within the pineal gland but diffuses into the capillary blood and cerebrospinal fluid (CSF) [Tricoire *et al.* 2003]. In a recent study conducted in humans, CSF melatonin levels were found to be higher in the third ventricle compared with the lateral one, thus indicating that melatonin enters the CSF through the pineal recess, even during daytime [Leston *et al.* 2010].

In all mammals pineal melatonin biosynthesis is synchronized to light/dark cycle by the SCN, which receives its input from the retinohypothalamic tract. Special photoreceptive retinal ganglion cells containing melanopsin as a photopigment are involved in the projection from retina [Berson *et al.* 2002; Brainard *et al.* 2001]. Fibers from the SCN pass through a circuitous route involving the paraventricular nucleus of the hypothalamus, medial forebrain bundle, reticular formation, lateral horn cells of the spinal cord, superior cervical ganglion, and then proceed to innervate pineal gland as post-ganglionic sympathetic fibers. NE released from these fibers regulate melatonin biosynthesis mainly through a β -adrenergic receptors–adenylyl cyclase–cyclic AMP mechanism [Klein *et al.* 1971].

In the circulation melatonin is partially bound to albumin [Cardinali *et al.* 1972], and can also bind to hemoglobin [Gilad and Zisapel, 1995]. Circulating melatonin is metabolized mainly in the liver where it is first hydroxylated by cytochrome P₄₅₀ mono-oxygenases (isoenzymes

CYP1B1, CYP1A2, CYP1A1) and thereafter conjugated with sulphate to be excreted as 6-sulfatoxymelatonin. Melatonin can be metabolized nonenzymatically in all cells of the body. It is converted into 3-hydroxymelatonin when it scavenges two hydroxyl radicals [Tan *et al.* 1998]. In the brain a substantial amount of melatonin can be metabolized to kynuramine derivatives [Hirata *et al.* 1974], especially under brain inflammatory conditions [Hardeland *et al.* 2009; Silva *et al.* 2005]. These metabolites of melatonin which are formed in the brain, namely, *N*¹-acetyl-*N*²-formyl-5-methoxy kynuramine (AFMK) and *N*¹-acetyl-5-methoxykynuramine (AMK), also share the antioxidant and anti-inflammatory properties of melatonin [Hardeland *et al.* 2009; Tan *et al.* 2001].

Melatonin exerts its physiological actions through G-protein MT₁ and MT₂ melatonin receptors expressed both singly and together in various cells and tissues of the body [Dubocovich *et al.* 2010]. Functional melatonin receptors have been localized in different areas of the brain such as the SCN [Liu *et al.* 1997], cerebellum [Al Ghoul *et al.* 1998], hippocampus [Savaskan *et al.* 2002] and central dopaminergic pathways, including the SN, caudate putamen, ventral tegmental areas, and nucleus accumbens [Uz *et al.* 2005]. MT₁ and MT₂ receptors, which have been found in the human amygdala and SN of normal subjects, have shown decreased expression in patients with PD [Adi *et al.* 2010].

Melatonin exerts some of its actions by binding to calmodulin [Benitez-King, 2006; Benitez-King and Anton-Tay, 1993], as well as to nuclear receptors of retinoic acid receptor family RZR β , ROR α -1, and ROR α -2 [Wiesenberg *et al.* 1998]. Melatonin's antioxidant actions comprise receptor-dependent and receptor-independent effects and, in particular, modulation of mitochondrial metabolism [Hardeland *et al.* 2011].

Melatonin is involved in the control of various physiological functions of the body such as seasonal control of reproductive processes [Srinivasan *et al.* 2009b; Reiter, 1980], sleep regulation [Wurtman and Zhdanova, 1995], immune mechanisms [Srinivasan *et al.* 2005; Guerrero and Reiter, 2002] and regulation of circadian [Deacon and Arendt, 1995; Armstrong, 1989] and sleep/wake rhythms [Arendt and Skene, 2005; Rajaratnam *et al.* 2004]. In addition to the above-mentioned physiological actions

melatonin in pharmacological doses inhibits tumor growth and may have a potential therapeutic value in treating breast cancer, prostate cancer, melanoma, and cancer of gastrointestinal tract [Srinivasan *et al.* 2008; Blask *et al.* 2005]. Melatonin also exerts antinociceptive and antiallostatic actions [Srinivasan *et al.* 2010]. As the prototype of the chronobiotic class of drugs [Cardinali *et al.* 2006; Arendt and Skene, 2005; Pévet *et al.* 2002; Dawson and Armstrong, 1996] melatonin restores the phase and amplitude of circadian rhythmicity by interaction with MT₁ and MT₂ receptors expressed in the SCN.

Conflicting results have been published on the circulating levels of melatonin in PD patients. In one study in which the levels of melatonin were measured twice daily at morning hours (10:00 and 12:00) the circulating melatonin levels from healthy subjects were lower than those of PD patients [Catala *et al.* 1997]. No information on nocturnal melatonin levels was provided in this study. Phase advances of the melatonin circadian rhythm were reported in PD patients [Bordet *et al.* 2003; Fertl *et al.* 1993, 1991] and a decrease in the amplitude of circulating melatonin rhythm was also observed [Bordet *et al.* 2003].

Owing to the lower rates of cancer mortality/incidence in patients with PD, speculations about risk or preventative factors common to both diseases, including lifestyle factors (such as smoking) and genetic susceptibility have been entertained [Rod *et al.* 2010]. Relevant to the subject of the present review is that preliminary epidemiological evidence suggests that longer years of working night shifts is associated with reduced melatonin levels and reduced risk of PD among whereas longer hours of sleep appear to increase their risk [Schernhammer *et al.* 2006]. While lower melatonin concentrations may predict a higher cancer risk [Stevens *et al.* 2011], there is also some evidence that they may be associated with a lower risk of PD.

Melatonin's neuroprotective role in animal models of Parkinson's disease

Animal models employed for studying the efficacy of various therapeutic agents in PD commonly produce behavioral deficits by suppressing brain dopaminergic function [Terzioglu and Galter, 2008; Schober, 2004]. This is achieved by injecting 6-hydroxydopamine (6-OHDA) into the nigrostriatal pathway of the

rat or by the systemic or intracerebral administration of neurotoxins such as MPTP, rotenone, or maneb–paraquat. The loss of dopamine neurons occurring in these animal models causes severe sensory and motor impairment which in turn gives rise to tremor, rigidity, and akinesia similar to those seen in PD patients [Terzioglu and Galter, 2008; Schober, 2004]. A major concern on these neurotoxin models is the obvious difference between models comprising attenuation of disease symptoms and models of the disease process itself, e.g. the α -synuclein knock out model [Ubhi *et al.* 2010; Rockenstein *et al.* 2007]. There is no information on melatonin efficacy to modify PD phenotype in genetic models of PD.

In a study using the MPTP model to produce PD symptoms, melatonin administration was found to counteract MPTP-induced lipid peroxidation in the striatum, hippocampal, and midbrain regions [Acuña-Castroviejo *et al.* 1997]. Using the same MPTP model, melatonin's ability to prevent neuronal cell death in the nigrostriatal pathway was demonstrated [Antolin *et al.* 2002].

MPTP elicits its neurotoxic effects by increasing the amount NO radicals derived from inducible nitric oxide synthase (iNOS) [Terzioglu and Galter, 2008; Schober, 2004]. The NO radicals act mainly on the cell bodies of dopamine neurons while NO radicals derived from the neuronal isoform of NOS (nNOS) damage the dopaminergic fibers and terminals in the striatum. Hence, it has been suggested that agents which inhibit the degenerative effects of iNOS stimulation in the SN should be considered as potential candidates for treating PD [Zhang *et al.* 2000]. Inasmuch as melatonin can effectively downregulate iNOS and prevent NO radical formation in the brain, it may have the potential to become a therapeutic agent in PD. The neuroprotective action of melatonin in the 6-OHDA animal model of PD has also been documented in other studies [Thomas and Mohanakumar, 2004; Dabbeni-Sala *et al.* 2001]. In addition, administration of melatonin in various doses (10–30 mg/kg) attenuated the rotenone-induced reduced glutathione depletion and increased the activity of the antioxidant enzymes superoxide dismutase and catalase in the nigrostriatal pathway [Saravanan *et al.* 2007].

It has been suggested that 6-OHDA could be generated in the brain after increasing dopamine

levels in excess and that the increased production of this neurotoxin could be the reason for selective degeneration of the SN in PD. Following levodopa administration, almost every cell in the brain having the aromatic amino acid decarboxylase enzyme will have an excess of dopamine, giving rise to high levels of 6-OHDA in the brain [Maharaj *et al.* 2005]. To examine the possibility that melatonin might prevent the formation of 6-OHDA *in vitro*, an experimental design using ferrous-ascorbate dopamine hydroxyl radical generating system, with addition of dopamine (1 mM) was employed [Borah and Mohanakumar, 2009]. The DA dependent production of 6-OHDA *in vitro* was decreased by melatonin in a dose-dependent manner. *In vivo*, daily administration of melatonin (30 mg/kg) along with levodopa was administered for seven consecutive days to mice and was found to reduce significantly the levodopa- or levodopa + MPTP-induced generation of striatal 6-OHDA [Borah and Mohanakumar, 2009].

Oxidative stress is known as one of the mechanisms of maneb- and paraquat-induced nigrostriatal dopaminergic neurodegeneration leading to PD phenotype. A recent study described melatonin efficacy to protect the SN of mice in this experimental model. Melatonin (30 mg/kg) for 9 weeks delayed degeneration, as indicated by changes in locomotor activity, striatal dopamine content, tyrosine hydroxylase immunoreactivity, number of degenerating neurons, lipid peroxidation, and nitrite content, as well as mRNA expression and catalytic activities of vesicular monoamine transporter, cytochrome P-450 2E1 and glutathione-S-transferase A4-4, and protein expressions of unphosphorylated and phosphorylated p53, Bax and caspase 9 [Singhal *et al.* 2011]. By downregulation of oxidative stress and the apoptotic pathway, melatonin displays nigrostriatal dopaminergic neuroprotection in mice.

It should be noted that contradictory results on the preventive role of melatonin in neurotoxin models of PD are also published. The chronic administration of pharmacological levels of melatonin did not ameliorate the MPTP-induced degeneration of the nigrostriatal pathway in mice [Morgan and Nelson, 2001; van der Schyf *et al.* 2000] and in one study [Willis and Armstrong, 1999] light exposure significantly reduced the severity of PD symptoms both under 6-OHDA and MPTP treatment of rats, whereas intracerebroventricular implants of slow

release melatonin increased the severity of the symptoms.

The alteration of circadian rhythms has been documented in animals with experimental lesions of basal ganglia [Mena-Segovia *et al.* 2002; Ben and Bruguierolle, 2000]. In rats receiving striatal injections of 6-OHDA, the amplitude of circadian rhythms in body temperature, heart rate, and activity rhythm was not altered, but the acrophase (i.e. the time of the maximum values in the rhythm) was advanced as compared with sham-lesioned controls [Ben and Bruguierolle, 2000]. In another study, Mena-Segovia and colleagues reported altered sleep/wake rhythms in striatum-lesioned rats, with increased wakefulness and reduced SWS and little modification of the rhythm's phase [Mena-Segovia *et al.* 2002].

Mitochondrial dysfunction in Parkinson's disease and the neuroprotective effects of melatonin

PD is a neurodegenerative disorder of multifactorial etiology. Among the several putative causal factors, oxidative stress and inflammation have been claimed to play a role in the loss of dopaminergic neurons [Maguire-Zeiss and Federoff, 2010; Tansey *et al.* 2007; Zhang *et al.* 1999]. The principal mediators of inflammatory responses in PD are the microglial cells which upon activation release inflammatory cytokines and reactive oxygen species [Tansey and Goldberg, 2010]. In addition, a dysfunctional blood–brain barrier also appears to be involved in the progression of the disease [Monahan *et al.* 2008; Zlokovic, 2008; Kortekaas *et al.* 2005].

The MPTP model of PD is a valuable tool for studying not only the participation of various factors such as oxidative/nitrosative stress, excitotoxicity, and inflammation in the pathogenesis of PD, but also for studying the role of mitochondrial dysfunction. MPTP is metabolized into MPP⁺ (1-methyl-4-phenyl pyridinium) which is taken up into the dopaminergic neurons through dopamine transporter and accumulates in the mitochondria of SN [Terzioglu and Galter, 2008; Schober, 2004]. MPP⁺ binds to Complex I of the electron transport chain (ETC) to inhibit it, thereby causing increased generation of reactive oxygen species. This results in oxidative damage to ETC, decreased ATP production and nigral cell death [Terzioglu and Galter, 2008; Schober, 2004]. MPP⁺, by inducing microglial activation and iNOS expression in

SN, has been shown to produce large amounts of NO and to cause neuronal cell death [Brown and Bal-Price, 2003]. NO, by reacting with O_2^- generates the highly toxic peroxynitrite, an agent that impairs mitochondrial function and causes irreversible inhibition of all ETC complexes [Brown and Borutaite, 2004] and neuronal cell death [Zhang *et al.* 2006].

Recently the participation of mitochondrial iNOS in the mitochondrial dysfunction and nigrostriatal degeneration was studied by using the MPTP model in mice [Tapias *et al.* 2009]. MPTP administration induced iNOS in the mitochondria of the dopamine neurons leading to high production of NO. Complex I inhibition, NO production and lipid peroxidation were all significantly higher after treatment with MPTP. Treatment with melatonin or AMK counteracted the effects of MPTP in brain nuclei, increasing Complex I activity above the control values in mitochondria. Both melatonin and AMK counteracted the effects of MPTP on lipid peroxidation and nitrite levels in the cytosol and the mitochondria of SN [Tapias *et al.* 2009]. A remarkable result of this study is that AMK, a brain metabolite of melatonin, was as efficient as melatonin treatment in counteracting i-mtNOS production, oxidative stress, and mitochondrial dysfunction induced by MPTP. The findings of this study raise the intriguing possibility of using kynuramines and related compounds from preventing Complex I dysfunction. Future directions of this study point out to the development of i-mtNOS antagonists such as AMT (2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine) or any other melatonin agonist may have significant value as therapeutic strategies for treating PD, and it is thus suggested that further research to explore this possibility should be undertaken.

Mitochondrial dysfunction is a cell biological characteristic of numerous neurodegenerative diseases and of PD, in particular [Acuña Castroviejo *et al.* 2011]. This has been demonstrated in detail using the cybrid (cytoplasmic hybrid) technique [Esteves *et al.* 2010; Borland *et al.* 2009; Keeney *et al.* 2009a, 2009b]. These studies convincingly showed defects in Complex I functioning of mitochondria obtained from PD patients. Improvements of Complex I activity by melatonin or AMK are, thus, not only relevant to models based on mitochondrial oxidotoxins, but potentially also to patients. Melatonin's property of enhancing Complex I activity has been also

demonstrated in otherwise untreated, normally aging and senescence-accelerated mouse strains [Carretero *et al.* 2009; Rodriguez *et al.* 2008; Okatani *et al.* 2003]. These data show that it would be a misconception to interpret melatonin's antioxidant actions only in terms of radical scavenging. Therefore, it is clearly different from other antioxidants, such as tocopherols, which are poorly effective in PD. Apart from its various additional effects on antioxidant enzymes and glutathione levels, melatonin reduces radical formation, e.g. by preventing excessive electron leakage at Complex I [Hardeland *et al.* 2011].

Melatonin as a therapeutic agent in Parkinson's disease

The finding that a reduced expression of melatonin MT_1 and MT_2 receptors occurs in amygdala and SN in patients with PD [Adi *et al.* 2010] indicates that there is a possibility that the melatonergic system is involved in the abnormal sleep mechanisms seen in PD as well as in its overall pathophysiology. Melatonin has been used for treating sleep problems, insomnia, and daytime sleepiness in PD patients. In a study undertaken on 40 PD patients (11 women, 29 men; range 43–76 years) melatonin was administered for a treatment period of 2 weeks, in doses ranging from 5 to 50 mg/day [Dowling *et al.* 2005]. To avoid the possibility of producing a circadian shift melatonin was administered 30 min before bedtime (circadian shifts can occur if melatonin is administered at any other time). All subjects were taking stable doses of antiparkinsonian medications during the course of the study. Relative to placebo, treatment with 50 mg of melatonin significantly increased night time sleep, as revealed by actigraphy. As compared with 50 mg or placebo, administration of 5 mg of melatonin was associated with significant improvement of sleep in the subjective reports. The study also found that the high dose of melatonin (50 mg) was well tolerated [Dowling *et al.* 2005].

In another study 18 patients were randomized after performing a basal PSG examination to receive melatonin (3 mg) or placebo 1 hour before bedtime for 4 weeks [Medeiros *et al.* 2007]. Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index and daytime somnolence by the Epworth Sleepiness Scale. All measures were repeated at the end of treatment. On initial assessment, 14 patients (70%) showed poor quality sleep and 8 patients (40%) showed EDS. Increased sleep latency (50%), REM sleep

without atonia (66%), and reduced sleep efficiency (72%) were found in PSG. Sleep fragmentation tended to be more severe in patients on lower doses of levodopa. Although melatonin significantly improved subjective quality of sleep PSG abnormalities remained unchanged. Motor dysfunction was not improved by the use of melatonin [Medeiros *et al.* 2007]. Although undetected differences in motor scores and PSG findings may have been due to the small sample size and a type II error, it must be noted that a significant divergence between PSG and subjective sleep evaluation had been reported in PD patients [Happe *et al.* 2005]. The findings that subjective more than objective findings of impaired sleep quality have a greater negative impact on life quality [Means *et al.* 2003] further suggest that PSG procedures may not be the best method for evaluating sleep disturbance in PD.

Melatonin 3–12 mg at bedtime has been shown to be effective in the treatment of RBD. This benefit has been reported in one case report [Kunz and Bes, 1997], two open-label prospective case series of patients with RBD [Takeuchi *et al.* 2001; Kunz and Bes, 1999] and two retrospective case series [Anderson and Shneerson, 2009; Boeve *et al.* 2003]. Taken together, these reports include a total of 38 patients. Out of these, 31 were noted to experience improvement with melatonin, 2 more experienced transient improvements and 1 seemed to worsen. Follow up as far as 25 months was reported. PSG showed statistically significant decreases in number of R epochs without atonia and in movement time in R. This contrasted with the persistence of tonic muscle tone in R sleep seen with patients treated with clonazepam. Owing to these data a recent clinical consensus recommended melatonin use in RBD at Level B, i.e. ‘assessment supported by sparse high-grade data or a substantial amount of low-grade data and/or clinical consensus by the task force’ [Aurora *et al.* 2010].

Exposure to light of 1000–1500 lux intensity for 1–1.5 h, 1 h prior to bedtime for 2–5 weeks has been found to improve the bradykinesia and rigidity observed in 12 PD patients [Willis and Turner, 2007]. A reduction in agitation and psychiatric side effects were also reported in this study. The authors suggested that activation of the circadian system by antagonizing melatonin secretion with bright light has a therapeutic value for treating the symptoms of PD [Willis, 2008].

At least one study performed in rats receiving 6-OHDA and MPTP treatment indicated that light exposure significantly reduced the severity of PD symptoms while intracerebroventricular melatonin implants increased the severity of the symptoms [Willis and Armstrong, 1999].

However, a number of observations contradict the conclusion that melatonin promotes PD. Bright light has been employed in a number of studies for treating depressive symptoms and the view has been advanced that suppression of melatonin secretion is not the likely mechanism by which artificial light exerts its therapeutic effect [Rosenthal *et al.* 1984]. Two possible mechanisms have been proposed for the therapeutic effect of bright light. First bright light could reset the phase of abnormal circadian rhythms seen in depressed patients [Lewy *et al.* 1984]. Secondly, although evening bright light exposure produces a momentary suppression of melatonin, it actually causes a rebound increase in melatonin secretion late in the night [Beck-Friis *et al.* 1985]. The fact that bright light exposure ultimately facilitates melatonin secretion rather than suppressing it is said to be responsible for the therapeutic efficacy of bright light in affective disorders. Hence, in the case of PD, bright light may improve the symptoms of PD, not by antagonizing melatonin secretion but by increasing it through a rebound effect.

The bright light effect may be indicative of circadian changes in PD. This may be supported by the reduced *Bmal1* mRNA expression in leukocytes [Cai *et al.* 2010b], although effects in peripheral oscillators do not necessarily allow conclusions on changes in the hypothalamic master clock. The recent finding that the mouse striatal dopamine receptors D1R and D2R are under circadian control [Cai *et al.* 2010a], can be seen as an interesting facet in this context, although circadian variations in receptor expression are by no means exceptional features. However, the conclusion that PD is a ‘melatonin hyperplasia’ disorder [Willis, 2008], is not supported by these findings. In this case, one would expect to find substantial elevations of melatonin in PD patients relative to age-matched controls, what has not been observed [Bordet *et al.* 2003; Sandyk, 1997; Fertl *et al.* 1993, 1991] and a decrease in the amplitude of circulating melatonin rhythm was also observed [Bordet *et al.* 2003]. Instead, melatonin receptor expression has been found to be reduced in the

PD SN [Adi *et al.* 2010] rather indicating a weakened melatonin signaling in this relevant area. If PD should turn out to be a circadian disorder, one would expect readjustments by melatonin rather than detrimental effects. However, in this case, this would be no longer a matter of dosage only, but even more that of appropriate circadian timing. In a disturbed circadian system, this may differ from that of healthy subjects and, therefore, require specific determinations of phase shifting effects by melatonin in PD patients.

Potential use of melatonin agonists in the treatment of Parkinson's disease

The available evidence indicates that both sleep induction as well as sleep maintenance at appropriate circadian phases are affected in PD patients. Moreover, the onset and timing of REM sleep is also very much impaired in PD patients [Naismith *et al.* 2010]. RBD seen in PD patients occurs much earlier and is predictive of dementia [Marion *et al.* 2008; Vendette *et al.* 2007]. Treatment of sleep disturbances in PD patients with appropriate drugs may help not only in solving sleep problems but may also help to prevent the progression of PD as well.

Since conventional drugs such as benzodiazepines, which are used for treating insomnia, may worsen the cognitive and memory impairment associated with PD, a hypnotic drug without any of these side effects merits consideration as a therapeutic alternative. Moreover, the finding that melatonin exerts its hypnotic and chronobiotic effects by acting through MT₁ and MT₂ receptors located in the SCN further supports the conclusion that it may have value as a therapy in PD. Although melatonin significantly improved subjective quality of sleep, PSG sleep abnormalities persisted in PD [Medeiros *et al.* 2008, 2007]. Since melatonin has a short half life (less than 30 minutes), a melatonin agonist with a longer duration of action and enhanced bioavailability might be of a greater benefit than melatonin in promoting sleep initiation.

Ramelteon is a novel melatonin receptor agonist that has been shown to act on MT₁ and MT₂ receptors, and has longer duration of action than melatonin [Kato *et al.* 2005]. The efficacy and safety of ramelteon in treating insomnia have been proven in a number of clinical studies conducted on elderly insomniacs [Richardson *et al.* 2009; Roth *et al.* 2007; Zammit *et al.* 2007; Erman *et al.* 2006]. Ramelteon may have

considerable therapeutic potential in treating the sleep problems including RBD seen in PD. Apart from treating sleep disturbances, ramelteon can alter the sleep/wake rhythm and can correct REM rhythm abnormality. Tasimelteon, another MT₁/MT₂ agonist in the process of evaluation, has also been shown to be effective for sleep resynchronization [Rajaratnam *et al.* 2009].

Depression is a common nonmotor symptom in PD. A review of 104 prevalence studies of depression in PD reported a prevalence of major depression of 17% and a prevalence of minor depression and dysthymia of 22 and 13%, respectively [Reijnders *et al.* 2008]. Depressive disorders may represent the first manifestation of PD years before the onset of motor symptoms [Postuma *et al.* 2010]. Almost two thirds of subjects meeting the criteria for depression are not treated with a clear impact on disability and on the increased need for symptomatic therapy of PD [Ravina *et al.* 2009].

PET studies have revealed a dysfunction of dopaminergic and noradrenergic central pathways in depressive Parkinsonian patients [Remy *et al.* 2005]. In addition, the involvement of the serotonergic system has been proposed, as shown by postmortem [Paulus and Jellinger, 1991] and PET [Boileau *et al.* 2008] studies. To what extent depression and sleep disorders are causally linked in PD patients is not known. Evidence from epidemiological and electroencephalographic studies implicate sleep disturbances as key factors in the pathogenesis of depressive illness [Lustberg and Reynolds, 2000]. Other evidence consistent with the circadian disruption hypothesis of depression comes from the observation that more than 80% of depressed patients have complaints of sleep disturbances and demonstrate a variety of PSG abnormalities [Riemann *et al.* 2001] and further that antidepressant therapies that also improve sleep efficiency are especially effective in reducing depressive symptomatology [Srinivasan *et al.* 2009a]. Moreover, detailed analyses have shown that currently used antidepressants such as selective serotonin reuptake inhibitors (SSRIs) exert adverse effects on sleep, and that the antidepressant effect may be counteracted by their effects on sleep [Lam, 2006; Moltzen and Bang-Andersen, 2006]. Hence, an ideal antidepressant in PD should improve sleep efficiency and reduce depressive symptomatology. Drugs such as nortryptine and other SSRIs, which have been employed to treat

depressive symptoms in PD, have not shown great effectiveness against the associated mood disturbances [Dobkin *et al.* 2010; Weintraub *et al.* 2010].

In this context it is worthwhile to mention the newly introduced melatonergic antidepressant, agomelatine. This drug has been tried in major depression disorders and has shown significant antidepressant activity in a number of clinical trials [Eser *et al.* 2010; Hale *et al.* 2010; Kasper *et al.* 2010; Zupancic and Guilleminault, 2006; Loo *et al.* 2002]. Agomelatine has a dually phased mechanism of action. At night its sleep-promoting melatonergic effects prevail over its potentially antihypnotic 5-HT_{2c} antagonism, while during the day, its antidepressant action via 5-HT_{2c} is uncoupled from melatonin's nocturnal actions. The sequential mode of action of agomelatine is its major therapeutic advantage over other agents in the antidepressant class [Pandi-Perumal *et al.* 2006a]. The use of agomelatine in PD may have considerable therapeutic potential because of its dual action for treating both the symptoms of depression and disturbed sleep. Since it also shares melatonin's chronobiotic properties, it may thus represent an ideal drug for treating PD.

Concluding remarks

At this time, there is no treatment to delay or stop the progression of PD. Rather, the medications currently available aim more towards the alleviation of PD symptoms. New surgical strategies may reversibly switch on the functionally damaged circuits through the electrical stimulation of deep brain structures. Nevertheless, while deep brain stimulation is a major advance in therapy, it is not suitable for all PD patients. New cell therapy approaches may be helpful in the future but are in a starting phase of design. Therefore, symptomatic medication will prevail for a while as a major approach for ameliorating the clinical signs of PD.

Nonmotor symptoms of PD such as RBD, occur in many PD patients, and predate the manifestation of motor symptoms. Their early diagnosis and treatment are essential for improving the quality of life in PD patients. Melatonin and melatonin agonists can be useful tools in treating sleep and associated disorders in PD. Although some of the suggestions put forward in the present manuscript are speculative, the available evidence supports the inference that melatonin

activity in PD can be substantial, and, further, that clinical investigations into the nature of this activity are warranted. This review comes at a critical time, as both preclinical and clinical studies strongly suggest melatonin's efficacy but further analysis is obviously needed. To what extent the therapeutic application of melatonin receptor agonists such as ramelteon or tasimelteon, or the melatonergic antidepressant agomelatine, is useful in PD deserves to be explored.

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References

- Acuña-Castroviejo, D., Coto-Montes, A., Gaia, M.M., Ortiz, G.G. and Reiter, R.J. (1997) Melatonin is protective against MPTP-induced striatal and hippocampal lesions. *Life Sci* 60: L23–L29.
- Acuña Castroviejo, D., Lopez, L.C., Escames, G., Lopez, A., Garcia, J.A. and Reiter, R.J. (2011) Melatonin-mitochondria Interplay in health and disease. *Curr Top Med Chem* 11: 221–240.
- Adi, N., Mash, D.C., Ali, Y., Singer, C., Shehadeh, L. and Papapetropoulos, S. (2010) Melatonin MT₁ and MT₂ receptor expression in Parkinson's disease. *Med Sci Monit* 16: BR61–BR67.
- Adler, C.H. (2005) Nonmotor complications in Parkinson's disease. *Mov Disord* 20(Suppl. 11): S23–S29.
- Adler, C.H. and Thorpy, M.J. (2005) Sleep issues in Parkinson's disease. *Neurology* 64: S12–S20.

- Al Ghoul, W.M., Herman, M.D. and Dubocovich, M.L. (1998) Melatonin receptor subtype expression in human cerebellum. *Neuroreport* 9: 4063–4068.
- Anderson, K.N. and Shneerson, J.M. (2009) Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. *J Clin Sleep Med* 5: 235–239.
- Antolin, I., Mayo, J.C., Sainz, R.M., del Brio, M.L., Herrera, F., Martin, V. *et al.* (2002) Protective effect of melatonin in a chronic experimental model of Parkinson's disease. *Brain Res* 943: 163–173.
- Arendt, J. and Skene, D.J. (2005) Melatonin as a chronobiotic. *Sleep Med Rev* 9: 25–39.
- Armstrong, S.M. (1989) Melatonin and circadian control in mammals. *Experientia* 45: 932–938.
- Arnulf, I., Konofal, E., Merino-Andreu, M., Houeto, J.L., Mesnage, V., Welter, M.L. *et al.* (2002) Parkinson's disease and sleepiness: an integral part of PD. *Neurology* 58: 1019–1024.
- Aurora, R.N., Zak, R.S., Maganti, R.K., Auerbach, S.H., Casey, K.R., Chowdhuri, S. *et al.* (2010) Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med* 6: 85–95.
- Beach, T.G., Adler, C.H., Lue, L., Sue, L.I., Bachalakuri, J., Henry-Watson, J. *et al.* (2009) Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol* 117: 613–634.
- Beck-Friis, J., Kjellman, B.F., Aperia, B., Uden, F., von Rosen, D., Ljunggren, J.G. *et al.* (1985) Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. *Acta Psychiatr Scand* 71: 319–330.
- Ben, V. and Bruguerolle, B. (2000) Effects of bilateral striatal 6-OHDA lesions on circadian rhythms in the rat: a radiotelemetric study. *Life Sci* 67: 1549–1558.
- Benitez-King, G. (2006) Melatonin as a cytoskeletal modulator: implications for cell physiology and disease. *J Pineal Res* 40: 1–9.
- Benitez-King, G. and Anton-Tay, F. (1993) Calmodulin mediates melatonin cytoskeletal effects. *Experientia* 49: 635–641.
- Berson, D.M., Dunn, F.A. and Takao, M. (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295: 1070–1073.
- Blask, D.E., Dauchy, R.T. and Sauer, L.A. (2005) Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. *Endocrine* 27: 179–188.
- Boeve, B.F., Dickson, D.W., Olson, E.J., Shepard, J.W., Silber, M.H., Ferman, T.J. *et al.* (2007a) Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med* 8: 60–64.
- Boeve, B.F., Silber, M.H. and Ferman, T.J. (2003) Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med* 4: 281–284.
- Boeve, B.F., Silber, M.H., Saper, C.B., Ferman, T.J., Dickson, D.W., Parisi, J.E. *et al.* (2007b) Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 130: 2770–2788.
- Boileau, I., Warsh, J.J., Guttman, M., Saint-Cyr, J.A., McCluskey, T., Rusjan, P. *et al.* (2008) Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [¹¹C]DASB. *Mov Disord* 23: 1776–1780.
- Borah, A. and Mohanakumar, K.P. (2009) Melatonin inhibits 6-hydroxydopamine production in the brain to protect against experimental parkinsonism in rodents. *J Pineal Res* 47: 293–300.
- Borbely, A.A. (1982) A two process model of sleep regulation. *Hum Neurobiol* 1: 195–204.
- Bordet, R., Devos, D., Brique, S., Touitou, Y., Guieu, J.D., Libersa, C. *et al.* (2003) Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. *Clin Neuropharmacol* 26: 65–72.
- Borland, M.K., Mohanakumar, K.P., Rubinstein, J.D., Keeney, P.M., Xie, J., Capaldi, R. *et al.* (2009) Relationships among molecular genetic and respiratory properties of Parkinson's disease cybrid cells show similarities to Parkinson's brain tissues. *Biochim Biophys Acta* 1792: 68–74.
- Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N. and Braak, E. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197–211.
- Braak, H., Sastre, M., Bohl, J.R., de Vos, R.A. and Del Tredici, K. (2007) Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. *Acta Neuropathol* 113: 421–429.
- Brainard, G.C., Hanifin, J.P., Rollag, M.D., Greeson, J., Byrne, B., Glickman, G. *et al.* (2001) Human melatonin regulation is not mediated by the three cone photopic visual system. *J Clin Endocrinol Metab* 86: 433–436.
- Brown, G.C. and Bal-Price, A. (2003) Inflammatory neurodegeneration mediated by nitric oxide, glutamate, and mitochondria. *Mol Neurobiol* 27: 325–355.
- Brown, G.C. and Borutaite, V. (2004) Inhibition of mitochondrial respiratory complex I by nitric oxide, peroxynitrite and S-nitrosothiols. *Biochim Biophys Acta* 1658: 44–49.
- Bruguerolle, B. and Simon, N. (2002) Biologic rhythms and Parkinson's disease: a chronopharmacologic approach to considering fluctuations in function. *Clin Neuropharmacol* 25: 194–201.

- Cai, Y., Ding, H., Li, N., Chai, Y., Zhang, Y. and Chan, P. (2010a) Oscillation development for neurotransmitter-related genes in the mouse striatum. *Neuroreport* 21: 79–83.
- Cai, Y., Liu, S., Sothorn, R.B., Xu, S. and Chan, P. (2010b) Expression of clock genes *Per1* and *Bmal1* in total leukocytes in health and Parkinson's disease. *Eur J Neurol* 17: 550–554.
- Cardinali, D.P., Furio, A.M., Reyes, M.P. and Brusco, L.I. (2006) The use of chronobiotics in the resynchronization of the sleep-wake cycle. *Cancer Causes Control* 17: 601–609.
- Cardinali, D.P., Lynch, H.J. and Wurtman, R.J. (1972) Binding of melatonin to human and rat plasma proteins. *Endocrinology* 91: 1213–1218.
- Carretero, M., Escames, G., Lopez, L.C., Venegas, C., Dayoub, J.C., Garcia, L. *et al.* (2009) Long-term melatonin administration protects brain mitochondria from aging. *J Pineal Res*, in press.
- Catala, M.D., Canete-Nicolas, C., Iradi, A., Tarazona, P.J., Tormos, J.M. and Pascual-Leone, A. (1997) Melatonin levels in Parkinson's disease: drug therapy versus electrical stimulation of the internal globus pallidus. *Exp Gerontol* 32: 553–558.
- Ceravolo, R., Rossi, C., Kiferle, L. and Bonuccelli, U. (2010) Nonmotor symptoms in Parkinson's disease: the dark side of the moon. *Future Neurology* 5: 851–871.
- Cermakian, N., Monaco, L., Pando, M.P., Dierich, A. and Sassone-Corsi, P. (2001) Altered behavioral rhythms and clock gene expression in mice with a targeted mutation in the *Period1* gene. *EMBO J* 20: 3967–3974.
- Chaudhuri, K.R., Healy, D.G. and Schapira, A.H. (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 5: 235–245.
- Chaudhuri, K.R., Pal, S., DiMarco, A., Whately-Smith, C., Bridgman, K., Mathew, R. *et al.* (2002) The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73: 629–635.
- Comella, C.L. (2006) Sleep disturbances and excessive daytime sleepiness in Parkinson disease: an overview. *J Neural Transm Suppl* 349–355.
- Comella, C.L. (2007) Sleep disorders in Parkinson's disease: an overview. *Mov Disord* 22(Suppl. 17): S367–S373.
- Compta, Y., Santamaria, J., Ratti, L., Tolosa, E., Iranzo, A., Munoz, E. *et al.* (2009) Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. *Brain* 132: 3308–3317.
- Dabbeni-Sala, F., Di Santo, S., Franceschini, D., Skaper, S.D. and Giusti, P. (2001) Melatonin protects against 6-OHDA-induced neurotoxicity in rats: a role for mitochondrial complex I activity. *FASEB J* 15: 164–170.
- Dawson, D. and Armstrong, S.M. (1996) Chronobiotics—drugs that shift rhythms. *Pharmacol Ther* 69: 15–36.
- Deacon, S. and Arendt, J. (1995) Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res* 688: 77–85.
- Dhawan, V., Dhoat, S., Williams, A.J., DiMarco, A., Pal, S., Forbes, A. *et al.* (2006a) 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 Neurol Sci* 248: 158–162.
- Dhawan, V., Healy, D.G., Pal, S. and Chaudhuri, K.R. (2006b) Sleep-related problems of Parkinson's disease. *Age Ageing* 35: 220–228.
- Dibner, C., Schibler, U. and Albrecht, U. (2010) The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol* 72: 517–549.
- Dijk, D.J., Shanahan, T.L., Duffy, J.F., Ronda, J.M. and Czeisler, C.A. (1997) Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J Physiol* 505: 851–858.
- Dobkin, R.D., Menza, M., Bienfait, K.L., Gara, M., Marin, H., Mark, M.H. *et al.* (2010) Depression in Parkinson's disease: symptom improvement and residual symptoms after acute pharmacologic management. *Am J Geriatr Psychiatry*, in press.
- Dowling, G.A., Mastick, J., Colling, E., Carter, J.H., Singer, C.M. and Aminoff, M.J. (2005) Melatonin for sleep disturbances in Parkinson's disease. *Sleep Med* 6: 459–466.
- Dubocovich, M.L., Delagrange, P., Krause, D.N., Sugden, D., Cardinali, D.P. and Olcese, J. (2010) International Union of Basic and Clinical Pharmacology. LXXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev* 62: 343–380.
- Edgar, D.M., Dement, W.C. and Fuller, C.A. (1993) Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 13: 1065–1079.
- Elbaz, A. and Moisan, F. (2008) Update in the epidemiology of Parkinson's disease. *Curr Opin Neurol* 21: 454–460.
- Erman, M., Seiden, D., Zammit, G., Sainati, S. and Zhang, J. (2006) An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Med* 7: 17–24.
- Erro, M.E., Moreno, M.P. and Zandio, B. (2010) [Pathophysiological bases of the non-motor symptoms in Parkinson's disease]. *Rev Neurol* 50(Suppl. 2): S7–S13.

- Eser, D., Baghai, T.C. and Moller, H.J. (2010) Agomelatine: The evidence for its place in the treatment of depression. *Core Evid* 4: 171–179.
- Esteves, A.R., Lu, J., Rodova, M., Onyango, I., Lezi, E., Dubinsky, R. *et al.* (2010) Mitochondrial respiration and respiration-associated proteins in cell lines created through Parkinson's subject mitochondrial transfer. *J Neurochem* 113: 674–682.
- Fahn, S. and Cohen, G. (1992) The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. *Ann Neurol* 32: 804–812.
- Fertl, E., Auff, E., Doppelbauer, A. and Waldhauser, F. (1991) Circadian secretion pattern of melatonin in Parkinson's disease. *J Neural Transm Park Dis Dement Sect 3*: 41–47.
- Fertl, E., Auff, E., Doppelbauer, A. and Waldhauser, F. (1993) Circadian secretion pattern of melatonin in de novo parkinsonian patients: evidence for phase-shifting properties of l-dopa. *J Neural Transm Park Dis Dement Sect 5*: 227–234.
- Friedman, J.H. and Chou, K.L. (2004) Sleep and fatigue in Parkinson's disease. *Parkinsonism Relat Disord* 10(Suppl. 1): S27–S35.
- Fukuya, H., Emoto, N., Nonaka, H., Yagita, K., Okamura, H. and Yokoyama, M. (2007) Circadian expression of clock genes in human peripheral leukocytes. *Biochem Biophys Res Commun* 354: 924–928.
- Garcia-Borreguero, D., Larrosa, O. and Bravo, M. (2003) Parkinson's disease and sleep. *Sleep Med Rev* 7: 115–129.
- Gibson, G.E., Starkov, A., Blass, J.P., Ratan, R.R. and Beal, M.F. (2010) Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. *Biochim Biophys Acta* 1802: 122–134.
- Gilad, E. and Zisapel, N. (1995) High-affinity binding of melatonin to hemoglobin. *Biochem Mol Med* 56: 115–120.
- Grandas, F. and Iranzo, A. (2004) Nocturnal problems occurring in Parkinson's disease. *Neurology* 63: S8–S11.
- Guerrero, J.M. and Reiter, R.J. (2002) Melatonin-immune system relationships. *Curr Top Med Chem* 2: 167–179.
- Hale, A., Corral, R.M., Mencacci, C., Ruiz, J.S., Severo, C.A. and Gentil, V. (2010) Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. *Int Clin Psychopharmacol* 25: 305–314.
- Happe, S., Klosch, G., Lorenzo, J., Kunz, D., Penzel, T., Roschke, J. *et al.* (2005) Perception of sleep: subjective versus objective sleep parameters in patients with Parkinson's disease in comparison with healthy elderly controls. Sleep perception in Parkinson's disease and controls. *J Neurol* 252: 936–943.
- Happe, S., Ludemann, P. and Berger, K. (2002) The association between disease severity and sleep-related problems in patients with Parkinson's disease. *Neuropsychobiology* 46: 90–96.
- Hardeland, R., Cardinali, D.P., Srinivasan, V., Spence, D.W., Brown, G.M. and Pandi-Perumal, S.R. (2011) Melatonin—a pleiotropic, orchestrating regulator molecule. *Progr Neurobiol* 93: 350–384.
- Hardeland, R., Tan, D.X. and Reiter, R.J. (2009) Kynuramines, metabolites of melatonin and other indoles: the resurrection of an almost forgotten class of biogenic amines. *J Pineal Res* 47: 109–116.
- Hilker, R., Razai, N., Ghaemi, M., Weisenbach, S., Rudolf, J., Szeliés, B. *et al.* (2003) [¹⁸F]fluorodopa uptake in the upper brainstem measured with positron emission tomography correlates with decreased REM sleep duration in early Parkinson's disease. *Clin Neurol Neurosurg* 105: 262–269.
- Hirata, F., Hayaishi, O., Tokuyama, T. and Seno, S. (1974) In vitro and in vivo formation of two new metabolites of melatonin. *J Biol Chem* 249: 1311–1313.
- Hobson, D.E., Lang, A.E., Martin, W.R., Razmy, A., Rivest, J. and Fleming, J. (2002) Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* 287: 455–463.
- Itoh, N., Masuo, Y., Yoshida, Y., Cynshi, O., Jishage, K. and Niki, E. (2006) γ -Tocopherol attenuates MPTP-induced dopamine loss more efficiently than α -tocopherol in mouse brain. *Neurosci Lett* 403: 136–140.
- Jahan, I., Hauser, R.A., Sullivan, K.L., Miller, A. and Zesiewicz, T.A. (2009) Sleep disorders in Parkinson's disease. *Neuropsychiatr Dis Treat* 5: 535–540.
- Kasper, S., Hajak, G., Wulff, K., Hoogendijk, W.J., Montejo, A.L., Smeraldi, E. *et al.* (2010) Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J Clin Psychiatry* 71: 109–120.
- Kato, K., Hirai, K., Nishiyama, K., Uchikawa, O., Fukatsu, K., Ohkawa, S. *et al.* (2005) Neurochemical properties of ramelteon (TAK-375), a selective MT₁/MT₂ receptor agonist. *Neuropharmacology* 48: 301–310.
- Kaynak, D., Kiziltan, G., Kaynak, H., Benbir, G. and Uysal, O. (2005) Sleep and sleepiness in patients with Parkinson's disease before and after dopaminergic treatment. *Eur J Neurol* 12: 199–207.
- Keeney, P.M., Dunham, L.D., Quigley, C.K., Morton, S.L., Bergquist, K.E. and Bennett Jr, J.P. (2009a) Cybrid models of Parkinson's disease show variable mitochondrial biogenesis and genotype-respiration relationships. *Exp Neurol* 220: 374–382.

- Keeney, P.M., Quigley, C.K., Dunham, L.D., Papageorge, C.M., Iyer, S., Thomas, R.R. *et al.* (2009b) Mitochondrial gene therapy augments mitochondrial physiology in a Parkinson's disease cell model. *Hum Gene Ther* 20: 897–907.
- Klein, D.C., Weller, J.L. and Moore, R.Y. (1971) Melatonin metabolism: neural regulation of pineal serotonin: acetyl coenzyme A N-acetyltransferase activity. *Proc Natl Acad Sci U S A* 68: 3107–3110.
- Kondratov, R.V., Kondratova, A.A., Gorbacheva, V.Y., Vykhovanets, O.V. and Antoch, M.P. (2006) Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. *Genes Dev* 20: 1868–1873.
- Kortekaas, R., Leenders, K.L., van Oostrom, J.C., Vaalburg, W., Bart, J., Willemsen, A.T. *et al.* (2005) Blood-brain barrier dysfunction in parkinsonian mid-brain in vivo. *Ann Neurol* 57: 176–179.
- Kunz, D. and Bes, F. (1997) Melatonin effects in a patient with severe REM sleep behavior disorder: case report and theoretical considerations. *Neuropsychobiology* 36: 211–214.
- Kunz, D. and Bes, F. (1999) 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* 14: 507–511.
- Lam, R.W. (2006) Sleep disturbances and depression: a challenge for antidepressants. *Int Clin Psychopharmacol* 21(Suppl. 1): S25–S29.
- Larsen, J.P. (2003) Sleep disorders in Parkinson's disease. *Adv Neurol* 91: 329–334.
- Lavie, P., Wajsbort, J. and Youdim, M.B. (1980) Deprenyl does not cause insomnia in parkinsonian patients. *Commun Psychopharmacol* 4: 303–307.
- Lees, A.J., Blackburn, N.A. and Campbell, V.L. (1988) The nighttime problems of Parkinson's disease. *Clin Neuropharmacol* 11: 512–519.
- Leston, J., Harthe, C., Brun, J., Mottolose, C., Mertens, P., Sindou, M. *et al.* (2010) Melatonin is released in the third ventricle in humans. A study in movement disorders. *Neurosci Lett* 469: 294–297.
- Lewy, A.J., Sack, R.A. and Singer, C.L. (1984) Assessment and treatment of chronobiologic disorders using plasma melatonin levels and bright light exposure: the clock-gate model and the phase response curve. *Psychopharmacol Bull* 20: 561–565.
- Liu, C., Weaver, D.R., Jin, X., Shearman, L.P., Pieschl, R.L., Gribkoff, V.K. *et al.* (1997) Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* 19: 91–102.
- Liu, S., Cai, Y., Sothorn, R.B., Guan, Y. and Chan, P. (2007) Chronobiological analysis of circadian patterns in transcription of seven key clock genes in six peripheral tissues in mice. *Chronobiol Int* 24: 793–820.
- Loo, H., Hale, A. and D'haenen, H. (2002) Determination of the dose of agomelatine, a melatonin agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol* 17: 239–247.
- Lustberg, L. and Reynolds, C.F. (2000) Depression and insomnia: questions of cause and effect. *Sleep Med Rev* 4: 253–262.
- Maguire-Zeiss, K.A. and Federoff, H.J. (2010) Future directions for immune modulation in neurodegenerative disorders: focus on Parkinson's disease. *J Neural Transm* 117: 1019–1025.
- Maharaj, H., Sukhdev, M.D., Scheepers, M., Mokokong, R. and Daya, S. (2005) L-DOPA administration enhances 6-hydroxydopamine generation. *Brain Res* 1063: 180–186.
- Marion, M.H., Qurashi, M., Marshall, G. and Foster, O. (2008) Is REM sleep behaviour disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? *J Neurol* 255: 192–196.
- Means, M.K., Edinger, J.D., Glenn, D.M. and Fins, A.I. (2003) Accuracy of sleep perceptions among insomnia sufferers and normal sleepers. *Sleep Med* 4: 285–296.
- Medeiros, C.A., Carvalhede de Bruin, P.F., Lopes, L.A., Magalhaes, M.C., de Lourdes, S.M. and Sales de Bruin, V. (2007) Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease: A randomized, double blind, placebo-controlled study. *J Neurol* 254: 459–464.
- Medeiros, C.A., Carvalhede de Bruin, P.F., Lopes, L.A., Magalhaes, M.C., de Lourdes, S.M. and Sales de Bruin, V. (2008) Melatonin in Parkinson's disease. *J Neurol* 255: 758.
- Mehta, S.H., Morgan, J.C. and Sethi, K.D. (2008) Sleep disorders associated with Parkinson's disease: role of dopamine, epidemiology, and clinical scales of assessment. *CNS Spectr* 13: 6–11.
- Mena-Segovia, J., Cintra, L., Prospero-Garcia, O. and Giordano, M. (2002) Changes in sleep-waking cycle after striatal excitotoxic lesions. *Behav Brain Res* 136: 475–481.
- Moltzen, E.K. and Bang-Andersen, B. (2006) Serotonin reuptake inhibitors: the corner stone in treatment of depression for half a century—a medicinal chemistry survey. *Curr Top Med Chem* 6: 1801–1823.
- Monahan, A.J., Warren, M. and Carvey, P.M. (2008) Neuroinflammation and peripheral immune infiltration in Parkinson's disease: an autoimmune hypothesis. *Cell Transplant* 17: 363–372.
- Monderer, R. and Thorpy, M. (2009) Sleep disorders and daytime sleepiness in Parkinson's disease. *Curr Neurol Neurosci Rep* 9: 173–180.
- Morgan, W.W. and Nelson, J.F. (2001) Chronic administration of pharmacological levels of melatonin

- does not ameliorate the MPTP-induced degeneration of the nigrostriatal pathway. *Brain Res* 921: 115–121.
- Naismith, S.L., Rogers, N.L., Mackenzie, J., Hickie, I.B. and Lewis, S.J. (2010) The relationship between actigraphically defined sleep disturbance and REM sleep behaviour disorder in Parkinson's Disease. *Clin Neurol Neurosurg* 112: 420–423.
- Nomura, T., Inoue, Y., Miyake, M., Yasui, K. and Nakashima, K. (2006) Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. *Mov Disord* 21: 380–384.
- Okatani, Y., Wakatsuki, A., Reiter, R.J. and Miyahara, Y. (2003) Acutely administered melatonin restores hepatic mitochondrial physiology in old mice. *Int J Biochem Cell Biol* 35: 367–375.
- Olanow, C.W. (1992) An introduction to the free radical hypothesis in Parkinson's disease. *Ann Neurol* 32(Suppl): S2–S9.
- 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.
- Ondo, W.G., Vuong, K.D. and Jankovic, J. (2002) Exploring the relationship between Parkinson disease and restless legs syndrome. *Arch Neurol* 59: 421–424.
- Pandi-Perumal, S.R., Srinivasan, V., Cardinali, D.P. and Monti, M.J. (2006a) Could agomelatine be the ideal antidepressant? *Expert Rev Neurother* 6: 1595–1608.
- Pandi-Perumal, S.R., Srinivasan, V., Maestroni, G.J.M., Cardinali, D.P., Poeggeler, B. and Hardeland, R. (2006b) Melatonin: Nature's most versatile biological signal? *FEBS J* 273: 2813–2838.
- Paulus, W. and Jellinger, K. (1991) The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol* 50: 743–755.
- Pérez Lloret, S., Rossi, M., Cardinali, D.P. and Merello, M. (2010) Activity-rest rhythm abnormalities in Parkinson's disease patients are related to dopaminergic therapy. *Int J Neurosci* 120: 11–16.
- Pérez Lloret, S., Rossi, M., Nouzeilles, M.I., Trenkwalder, C., Carreras, L.O. and Merello, M. (2009) Parkinson's disease sleep scale, sleep logs, and actigraphy in the evaluation of sleep in parkinsonian patients. *J Neurol* 256: 1480–1484.
- Pévet, P., Bothorel, B., Slotten, H. and Saboureau, M. (2002) The chronobiotic properties of melatonin. *Cell Tissue Res* 309: 183–191.
- Postuma, R.B., Gagnon, J.F. and Montplaisir, J. (2010) Clinical prediction of Parkinson's disease: planning for the age of neuroprotection. *J Neurol Neurosurg Psychiatry* 81: 1008–1013.
- Rajaratnam, S.M., Middleton, B., Stone, B.M., Arendt, J. and Dijk, D.J. (2004) Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *J Physiol* 561: 339–351.
- Rajaratnam, S.M., Polymeropoulos, M.H., Fisher, D.M., Roth, T., Scott, C., Birznieks, G. et al. (2009) Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 373: 482–491.
- Ravina, B., Elm, J., Camicioli, R., Como, P.G., Marsh, L., Jankovic, J. et al. (2009) The course of depressive symptoms in early Parkinson's disease. *Mov Disord* 24: 1306–1311.
- Reijnders, J.S., Ehrt, U., Weber, W.E., Aarsland, D. and Leentjens, A.F. (2008) A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 23: 183–189.
- Reiter, R.J. (1980) The pineal and its hormones in the control of reproduction in mammals. *Endocr Rev* 1: 109–131.
- Reiter, R.J., Tan, D.X. and Fuentes-Broto, L. (2010) Melatonin: a multitasking molecule. *Prog Brain Res* 181: 127–151.
- Remy, P., Doder, M., Lees, A., Turjanski, N. and Brooks, D. (2005) Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128: 1314–1322.
- Richardson, G.S., Zammit, G., Wang-Weigand, S. and Zhang, J. (2009) Safety and subjective sleep effects of ramelteon administration in adults and older adults with chronic primary insomnia: a 1-year, open-label study. *J Clin Psychiatry* 70: 467–476.
- Riemann, D., Berger, M. and Voderholzer, U. (2001) Sleep and depression—results from psychobiological studies: an overview. *Biol Psychol* 57: 67–103.
- Rockenstein, E., Crews, L. and Masliah, E. (2007) Transgenic animal models of neurodegenerative diseases and their application to treatment development. *Adv Drug Deliv Rev* 59: 1093–1102.
- Rod, N.H., Hansen, J., Schernhammer, E. and Ritz, B. (2010) Major life events and risk of Parkinson's disease. *Mov Disord* 25: 1639–1645.
- Rodriguez, M.I., Escames, G., Lopez, L.C., Lopez, A., Garcia, J.A., Ortiz, F. et al. (2008) Improved mitochondrial function and increased life span after chronic melatonin treatment in senescent prone mice. *Exp Gerontol* 43: 749–756.
- Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y. et al. (1984) Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 41: 72–80.
- Roth, T., Seiden, D., Wang-Weigand, S. and Zhang, J. (2007) A 2-night, 3-period, crossover study of

- ramelteon's efficacy and safety in older adults with chronic insomnia. *Curr Med Res Opin* 23: 1005–1014.
- Sack, R.L., Lewy, A.J., Blood, M.L., Keith, L.D. and Nakagawa, H. (1992) Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. *J Clin Endocrinol Metab* 75: 127–134.
- Sandyk, R. (1997) The accelerated aging hypothesis of Parkinson's disease is not supported by the pattern of circadian melatonin secretion. *Int J Neurosci* 90: 271–275.
- Saper, C.B., Lu, J., Chou, T.C. and Gooley, J. (2005) The hypothalamic integrator for circadian rhythms. *Trends Neurosci* 28: 152–157.
- Saravanan, K.S., Sindhu, K.M. and Mohanakumar, K.P. (2007) Melatonin protects against rotenone-induced oxidative stress in a hemiparkinsonian rat model. *J Pineal Res* 42: 247–253.
- Savaskan, E., Olivieri, G., Meier, F., Brydon, L., Jockers, R., Ravid, R. *et al.* (2002) Increased melatonin 1a-receptor immunoreactivity in the hippocampus of Alzheimer's disease patients. *J Pineal Res* 32: 59–62.
- Savica, R., Rocca, W.A. and Ahlskog, J.E. (2010) When does Parkinson disease start? *Arch Neurol* 67: 798–801.
- Scaravilli, T., Gasparoli, E., Rinaldi, F., Polesello, G. and Bracco, F. (2003) Health-related quality of life and sleep disorders in Parkinson's disease. *Neurol Sci* 24: 209–210.
- Scheer, F.A., Wright Jr, K.P., Kronauer, R.E. and Czeisler, C.A. (2007) Plasticity of the intrinsic period of the human circadian timing system. *PLoS ONE* 2: e721.
- Schenck, C.H., Bundlie, S.R. 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 behaviour disorder. *Neurology* 46: 388–393.
- Schernhammer, E., Chen, H. and Ritz, B. (2006) Circulating melatonin levels: possible link between Parkinson's disease and cancer risk? *Cancer Causes Control* 17: 577–582.
- Schober, A. (2004) Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res* 318: 215–224.
- Shiba, M., Bower, J.H., Maraganore, D.M., McDonnell, S.K., Peterson, B.J., Ahlskog, J.E. *et al.* (2000) Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. *Mov Disord* 15: 669–677.
- Silva, S.O., Ximenes, V.F., Livramento, J.A., Catalani, L.H. and Campa, A. (2005) High concentrations of the melatonin metabolite, N1-acetyl-N2-formyl-5-methoxykynuramine, in cerebrospinal fluid of patients with meningitis: a possible immunomodulatory mechanism. *J Pineal Res* 39: 302–306.
- Simuni, T. (2004) Somnolence and other sleep disorders in Parkinson's disease: the challenge for the practicing neurologist. *Neurol Clin* 22: S107–S126.
- Singhal, N.K., Srivastava, G., Patel, D.K., Jain, S.K. and Singh, M.P. (2011) Melatonin or silymarin reduces maneb- and paraquat-induced Parkinson's disease phenotype in the mouse. *J Pineal Res* 50: 97–109.
- Srinivasan, V., Maestroni, G., Cardinali, D., Esquifino, A., Perumal, S.P. and Miller, S. (2005) Melatonin, immune function and aging. *Immun Ageing* 2: 17.
- Srinivasan, V., Pandi-Perumal, S.R., Spence, D.W., Moscovitch, A., Trakht, I., Brown, G.M. *et al.* (2010) Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull* 81: 362–371.
- Srinivasan, V., Pandi-Perumal, S.R., Trakht, I., Spence, D.W., Hardeland, R., Poeggeler, B. *et al.* (2009a) Pathophysiology of depression: role of sleep and the melatonergic system. *Psychiatry Res* 165: 201–214.
- Srinivasan, V., Spence, D.W., Pandi-Perumal, S.R., Trakht, I. and Cardinali, D.P. (2008) Therapeutic actions of melatonin in cancer: possible mechanisms. *Integrative Cancer Therapies* 7: 189–203.
- Srinivasan, V., Spence, W.D., Pandi-Perumal, S.R., Zakharia, R., Bhatnagar, K.P. and Brzezinski, A. (2009b) Melatonin and human reproduction: shedding light on the darkness hormone. *Gynecol Endocrinol* 25: 779–785.
- Stevens, R.G., Hansen, J., Costa, G., Haus, E., Kauppinen, T., Aronson, K.J. *et al.* (2011) Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 68: 154–162.
- Suzuki, K., Okuma, Y., Hattori, N., Kamei, S., Yoshii, F., Utsumi, H. *et al.* (2007) Characteristics of sleep disturbances in Japanese patients with Parkinson's disease. A study using Parkinson's disease sleep scale. *Mov Disord* 22: 1245–1251.
- Takeuchi, N., Uchimura, N., Hashizume, Y., Mukai, M., Etoh, Y., Yamamoto, K. *et al.* (2001) Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci* 55: 267–269.
- Tan, D.X., Manchester, L.C., Burkhardt, S., Sainz, R.M., Mayo, J.C., Kohen, R. *et al.* (2001) N1-acetyl-N2-formyl-5-methoxykynuramine, a biogenic amine and melatonin metabolite, functions as a potent antioxidant. *FASEB J* 15: 2294–2296.
- Tan, D.X., Manchester, L.C., Reiter, R.J., Plummer, B.F., Hardies, L.J., Weintraub, S.T. *et al.* (1998) A novel melatonin metabolite, cyclic 3-hydroxymelatonin: a biomarker of in vivo hydroxyl radical generation. *Biochem Biophys Res Commun* 253: 614–620.
- Tandberg, E., Larsen, J.P. and Karlsen, K. (1999) Excessive daytime sleepiness and sleep benefit in

- Parkinson's disease: a community-based study. *Mov Disord* 14: 922–927.
- Tansey, M.G. and Goldberg, M.S. (2010) Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. *Neurobiol Dis* 37: 510–518.
- Tansey, M.G., McCoy, M.K. and Frank-Cannon, T.C. (2007) Neuroinflammatory mechanisms in Parkinson's disease: potential environmental triggers, pathways, and targets for early therapeutic intervention. *Exp Neurol* 208: 1–25.
- Tapias, V., Escames, G., Lopez, L.C., Lopez, A., Camacho, E., Carrion, M.D. *et al.* (2009) Melatonin and its brain metabolite *N*¹-acetyl-5-methoxykynuramine prevent mitochondrial nitric oxide synthase induction in parkinsonian mice. *J Neurosci Res* 87: 3002–3010.
- Terzioglu, M. and Galter, D. (2008) Parkinson's disease: genetic versus toxin-induced rodent models. *FEBS J* 275: 1384–1391.
- Thannickal, T.C., Lai, Y.Y. and Siegel, J.M. (2007) Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* 130: 1586–1595.
- Thannickal, T.C., Lai, Y.Y. and Siegel, J.M. (2008) Hypocretin (orexin) and melanin concentrating hormone loss and the symptoms of Parkinson's disease. *Brain* 131: e87.
- The Parkinson Study Group. (1993) Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group. *N Engl J Med* 328: 176–183.
- Thomas, B. and Mohanakumar, K.P. (2004) Melatonin protects against oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the mouse nigrostriatum. *J Pineal Res* 36: 25–32.
- Trenkwalder, C. (1998) Sleep dysfunction in Parkinson's disease. *Clin Neurosci* 5: 107–114.
- Tricoire, H., Moller, M., Chemineau, P. and Malpoux, B. (2003) Origin of cerebrospinal fluid melatonin and possible function in the integration of photoperiod. *Reprod Suppl* 61: 311–321.
- Ubhi, K., Rockenstein, E., Mante, M., Inglis, C., Adame, A., Patrick, C. *et al.* (2010) Alpha-synuclein deficient mice are resistant to toxin-induced multiple system atrophy. *Neuroreport* 21: 457–462.
- Uz, T., Arslan, A.D., Kurtuncu, M., Imbesi, M., Akhisaroglu, M., Dwivedi, Y. *et al.* (2005) The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. *Brain Res Mol Brain Res* 136: 45–53.
- van der Schyf, C.J., Castagnoli, K., Palmer, S., Hazelwood, L. and Castagnoli Jr, N. (2000) Melatonin fails to protect against long-term MPTP-induced dopamine depletion in mouse striatum. *Neurotox Res* 1: 261–269.
- van Hilten, B., Hoff, J.I., Middelkoop, H.A., van der Velde, E.A., Kerkhof, G.A., Wauquier, A. *et al.* (1994) Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. *Arch Neurol* 51: 922–928.
- Vendette, M., Gagnon, J.F., Decary, A., Massicotte-Marquez, J., Postuma, R.B., Doyon, J. *et al.* (2007) REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology* 69: 1843–1849.
- Wehr, T.A., Aeschbach, D. and Duncan Jr, W.C. (2001) Evidence for a biological dawn and dusk in the human circadian timing system. *J Physiol* 535: 937–951.
- Weintraub, D., Mavandadi, S., Mamikonyan, E., Siderowf, A.D., Duda, J.E., Hurtig, H.I. *et al.* (2010) Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology* 75: 448–455.
- Weintraub, D., Moberg, P.J., Duda, J.E., Katz, I.R. and Stern, M.B. (2004) Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc* 52: 784–788.
- Weisskopf, M.G., Chen, H., Schwarzschild, M.A., Kawachi, I. and Ascherio, A. (2003) Prospective study of phobic anxiety and risk of Parkinson's disease. *Mov Disord* 18: 646–651.
- Wiesenberg, I., Missbach, M. and Carlberg, C. (1998) The potential role of the transcription factor RZR/ROR as a mediator of nuclear melatonin signaling. *Restor Neurol Neurosci* 12: 143–150.
- Willis, G.L. (2008) Parkinson's disease as a neuroendocrine disorder of circadian function: dopamine-melatonin imbalance and the visual system in the genesis and progression of the degenerative process. *Rev Neurosci* 19: 245–316.
- Willis, G.L. and Armstrong, S.M. (1999) A therapeutic role for melatonin antagonism in experimental models of Parkinson's disease. *Physiol Behav* 66: 785–795.
- Willis, G.L. and Turner, E.J. (2007) Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. *Chronobiol Int* 24: 521–537.
- Wu, Y., Le, W. and Jankovic, J. (2011) Preclinical biomarkers of Parkinson disease. *Arch Neurol* 68: 22–30.
- Wurtman, R.J. and Zhdanova, I. (1995) Improvement of sleep quality by melatonin. *Lancet* 346: 1491.
- Young, A., Home, M., Churchward, T., Freezer, N., Holmes, P. and Ho, M. (2002) Comparison of sleep disturbance in mild versus severe Parkinson's disease. *Sleep* 25: 573–577.
- Zammit, G., Erman, M., Wang-Weigand, S., Sainati, S., Zhang, J. and Roth, T. (2007) Evaluation of the efficacy and safety of ramelteon in

subjects with chronic insomnia. *J Clin Sleep Med* 3: 495–504.

Zhang, J., Perry, G., Smith, M.A., Robertson, D., Olson, S.J., Graham, D.G. *et al.* (1999) Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. *Am J Pathol* 154: 1423–1429.

Zhang, L., Dawson, V.L. and Dawson, T.M. (2006) Role of nitric oxide in Parkinson's disease. *Pharmacol Ther* 109: 33–41.

Zhang, Y., Dawson, V.L. and Dawson, T.M. (2000) Oxidative stress and genetics in the pathogenesis of Parkinson's disease. *Neurobiol Dis* 7: 240–250.

Zlokovic, B.V. (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 57: 178–201.

Zupancic, M. and Guilleminault, C. (2006) Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 20: 981–992.

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