Melatonin Therapy of RBD

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24.1 Introduction

In 1995 we used melatonin as a treatment for rapid eye movement (REM) sleep behavior disorder (RBD) for the first time [1]. A 64-year-old man with the clinically and polysomnographically (PSG) confirmed diagnosis of RBD also suffered from insomnia (having troubles with both initiating and maintaining sleep) with excessive daytime tiredness and impairment of short-time memory. Due to the patient's comorbidity, clonazepam was not considered to be a good initial treatment option, and so melatonin therapy was begun with a dose of 3 mg within 30 min before bedtime. Surprisingly, over weeks not only general sleep abnormalities and cognitive/amnestic deficits but also the RBD symptoms showed a complete clinical recovery. A second PSG study after 2 months of treatment showed no major changes in sleep structure, except an increase of REM sleep (13% vs. 17% of sleep period time) and a better qualitative preservation of REM sleep-associated muscle atonia with a reduction of REM epochs with movement time to almost half of the baseline. Actigraphic data showed that in the first 2 weeks of melatonin treatment, movement parameters during time in bed generally decreased to about 70% of baseline value and that after 5 months of treatment, these parameters were reduced even further to about 40% of baseline value. Clinical symptoms gradually returned 3 weeks after the end of treatment starting with yelling and a first episode of jumping out of bed 3 months after melatonin discontinuation. Thereafter, treatment was resumed.

In this chapter, we summarize our own experience and the cumulative published data on the treatment of RBD patients with melatonin and melatonergic agonists. Also we cite evidence for our hypothesis that one basic mode of therapeutic action is on the influence of melatonin on RBD symptoms via the circadian timing system.

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24.2 Melatonin and Melatonergic Agonists: Actions and Metabolisms in the CNS

Looking into the physiology, melatonin, *N*-acetyl-5-methoxytryptamine, first isolated 1958 by Lerner and colleagues in bovine pineal glands, is a product of tryptophan metabolism [2]. It is mainly secreted by the pineal gland but also produced by other tissues, such as the retina, lymphocytes, and gastrointestinal tract.

Melatonin release follows a marked circadian rhythm, controlled by the hypothalamic suprachiasmatic nucleus (SCN) as the central circadian pacemaker or master clock. The SCN receives its timekeeping input mainly from the retinohypothalamic tract.

Special photoreceptive retinal ganglion cells, containing the photopigment melanopsin, are involved in the projection from the retina. Highest melatonin levels occur during the night and transduce the information "darkness" as a feedback signal to the SCN, for readjusting the clock [3], and to other inferior central and peripheral circadian oscillators.

Melatonin has high accessibility throughout the body due to its amphiphilic nature. It exerts its physiological effects through activation of at least two high-affinity G-protein-coupled receptors MT_1 and MT_2, which show distinct molecular structures, pharmacological characteristics, and anatomical distribution patterns. Tissues with MT_1 and MT_2 receptors include the retina, cerebral cortex, hypothalamus, midbrain, periaqueductal gray, cerebellum, hippocampus, ovaries, cerebral and peripheral arteries, kidneys, pancreas, adipocytes, and immune cells [4, 5]. Cerebral tissues with mainly MT_1 receptors include the SCN, pituitary gland pars tuberalis, habenula, dorsal raphe nucleus, superior colliculi, and substantia nigra pars compacta; those with mainly MT_2 receptors include the reticular thalamic nucleus, inferior colliculi, and substantia nigra pars reticulata [5]. Physiologically, MT_1 and MT_2 receptors have distinctive functional roles. In rodents, circadian phase shifting is preferentially mediated through activation of the MT_1 receptor, as demonstrated using MT_1 knockout mice in a model of circadian re-entrainment [6]. It has been shown that MT_1 may also modulate biological clock-related gene expressions, as the expression of most clock genes in the pituitary gland is reduced in MT_1 knockout mice but not in MT_2 knockout mice [7]. Additional evidence exists that melatonin action in the SCN can be attributed to mainly MT_1 receptors with only a minimal role for MT_2 [8]. Further experiments with MT_1 and MT_2 knockout mice indicate that each melatonin receptor subtype differently regulates the vigilance states: MT_2 receptors mainly non-rapid eye movement (NREM) sleep and MT_1 receptors mainly REM sleep [9].

Phase and amplitude of SCN neuronal activity rhythm can be alternately stimulated by light and melatonin just like a clock pendulum [10]. The involvement of melatonin in circadian regulation can not only be observed on the cellular and neuronal level but also in the modulation of a wide variety of highly relevant physiological functions [11, 12]. Besides the well-known chronobiotic and sleep-facilitating properties in diurnal species, many other physiological effects have been attributed to melatonin, such as modulation of other hormone secretions and enhancement of

immunological functioning. Other functions of melatonin include anti-inflammatory, cancer protective, glucose regulatory, and neuroprotective, as well as free-radical scavenging and antioxidant properties [13, 14].

Orally administered melatonin has a short half-life of approximately 1 h and a low bioavailability of 15% [15]. It is well tolerated without significant side effects, even up to very high doses. In a phase I dose escalation study in healthy volunteers to assess the tolerability and pharmacokinetics of 20, 30, 50, and 100 mg oral doses of melatonin, no adverse effects other than mild transient drowsiness with no effects on sleeping patterns were seen [16]. Circulating melatonin is metabolized in the liver, mainly by the cytochrome P450 enzyme CYP1A2, to its primary metabolite 6-hydroxymelatonin and after conjugation with sulfate excreted in urine. Decreased CYP1A2 activity in the liver either genetically determined or from concomitant medication, hence, can slow down melatonin metabolism. The proportion of individuals with a slow CYP1A2 phenotype is about 13% [17] but may vary among ethnic populations. With patients who are slow metabolizers in this respect, the ingestion of the usual doses of exogenous melatonin can thus result in accumulation and, by consequence, to loss of its circadian variation, which eventually leads to a loss of effectiveness [18]. Decreasing the dose or intermittent melatonin administration every other day can remedy this.

During the last decade, the therapeutic potential of melatonin in a wide variety of clinical conditions has become an area of great interest, leading to the development of new agents, including prolonged-release melatonin and selective melatonin receptor agonists.

Prolonged-release melatonin (Circadin®) was approved in Europe by the European Medicines Agency (EMA) 2007 as monotherapy for the short-term treatment of primary insomnia in patients of 55 years and over and is currently commercialized in Europe and Asia-Pacific territories [19]. Agomelatine (Valdoxan®) is a melatonin MT_1 and MT_2 receptor agonist, and a weak 5-HT_{2C} antagonist received marketing authorization in the European Union in 2009 and Therapeutic Goods Administration (TGA) approval for marketing in Australia in August 2010 for the treatment of depression, whereas the development for the US market was discontinued in October 2011 [19, 20]. Ramelteon (Rozerem®) is a melatonin MT_1 and MT_2 receptor agonist, which has been approved by the US Food and Drug Administration (FDA) 2005 for the treatment of insomnia [19, 20]. Tasimelteon (Hetlioz®) is another selective agonist for the melatonin receptors MT_1 and MT_2, approved by the FDA and since 2015 in Europe by the EMA solely for the treatment of non-24-h sleep-wake disorder [19, 21].

24.3 Melatonin and Melatonergic Agonists as Treatment Options for RBD

Our first findings were confirmed in an open-labeled trial with six patients (melatonin 3 mg within 30 min before bedtime) and also in a randomized, double-blind, placebo-controlled trial in a crossover design with eight patients (placebo or

melatonin 3 mg within 30 min before bedtime), each for a period of 4 weeks [22, 23]. The diagnosis of RBD was confirmed clinically and with time-synchronized video-PSG (vPSG). Twelve of 14 patients showed a clear clinical improvement within weeks. Eleven patients no longer experienced enacting of dreams. Another responder reported a reduction of RBD episodes from every night to once a week only. None of these responders reported any frightening dreams during melatonin treatment. After discontinuation of melatonin, RBD symptoms returned only in some patients after weeks to months. The electromyogram (EMG) of the PSG at the end of melatonin treatment showed significantly decreased REM sleep without atonia (RWA; from 32% down to 11% [22] and from 39% down to 27% [23]), while phasic activity during REM sleep was unchanged. Interestingly, in the placebo-controlled crossover study, we nevertheless found a better preservation of muscle atonia at the end of the placebo phase, but only in those patients who were treated with melatonin in the earlier verum phase. Due to the crossover design, the control vPSG for those patients was performed 5 weeks after discontinuation of melatonin treatment. Apparently melatonin effects persist after treatment discontinuation, which might have some clinical relevance.

Since then, a few more case reports, small case series, retrospective case reviews, and one randomized, placebo-controlled crossover study on the efficacy and tolerability of melatonin and melatonergic agonists for the treatment of RBD have been published (summarized in Table 24.1 for melatonin and in Table 24.2 for melatonergic agonists).

Anecdotal evidence for melatonin effects on RBD is provided by a prospective observational study performed by Takeuchi et al. [24]. They examined effects of melatonin in 15 patients with vPSG confirmed RBD, but without provision of further information regarding comorbidities, including possible obstructive sleep apnea (OSA), or duration of melatonin treatment and follow-up. Melatonin dose was 3–9 mg administered 30 min before bedtime. Thirteen patients reported a mild to strong improvement of symptoms. The authors reported a dose dependency of observed effect in some patients without providing further data. In the melatonin responders, efficacy was investigated by vPSG. Melatonin administration significantly reduced the percentage of tonic REM activity (from 16 to 6%) while leaving all other sleep variables in vPSG unchanged. In addition, drug levels were measured at baseline and at 3 h after administration. The investigators found a higher response in patients with lower baseline melatonin levels.

In a retrospective observational study, Boeve et al. confirmed the efficacy of melatonin monotherapy as well as combined therapy with clonazepam. They examined 14 selected patients with "RBD associated with several neurologic conditions," after clonazepam either had failed, showed significant side effects, or was contraindicated [25]. One half of the patients still took clonazepam (0.5–1 mg/night) in addition to melatonin; the other half converted to melatonin monotherapy. Ten patients showed marked clinical improvement, five of them combined with clonazepam. The melatonin responders showed an improvement concerning nightmares, which tended to correlate with the improvement in dream enactment behaviors. The effective dose of melatonin ranged from 3 to 12 mg taken at bedtime. Side effects

Table 24.1 Effects of melatonin on RBD symptoms

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* responding (based on patients and bedpartners' reports)	vPSG
Kunz et al. (1997) [1]	Case report, ICSD-2	1	64 y-old male, iRBD	Melatonin 3 mg per night, 5 months	1	↑%REM sleep, ↓RWA and ↓phasic EMG levels in REM
Kunz et al. (1999) [22]	Case series, ICSD-2	6	Three males, mean age 54 y, range 26–71 y, one PD, three of six with memory and concentration deficits	Melatonin 3 mg per night, 6 weeks	5	Significant ↑ REM atonia, significant ↓ stage shifts + MT in REM epochs
Kunz et al. (2010) [23]	RCT, crossover design, ICSD-2	8	Eight males, mean age 54 y, range 26–67 y, two narcolepsia, one PD	Placebo/melatonin 3 mg for 4 weeks, switch from the placebo to verum group or vice versa for another 4 weeks	7, significant improvement in CGI	Significant ↓ of RWA in the melatonin group, extended beyond the placebo part, if melatonin given first
Takeuchi et al. (2001) [24]	Case series, ICSD-1	15	Fourteen males, mean age 63.5 y, RBD with no further disclosures	Melatonin 3–9 mg per night, duration NM	13	↓Tonic REM activity
Boeve et al. (2003) [25]	Retrospective review, ICSD-R	14	Thirteen males, median RBD onset age 56 y, range 22–77 y, seven LBD, two MCI, two narcolepsia, one PD	Melatonin 3–12 mg per night +/− clonazepam 0.5–1 mg in seven patients, duration NM	10, 5/10 patients with concomitant clonazepam	ND

(continued)

Table 24.1 (continued)

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* responding (based on patients and bedpartners' reports)	vPSG
Anderson et al. (2009) [32]	Retrospective review, ICSD-2	2/39[a]	Thirty-eight males, mean age 66 y, range 34–86 y, one MCI + mild OSA	Melatonin 10 mg per night in 2/39 patients, 20 months. 37/39 other drug therapies	2	ND
McCarter et al. (2012) [26]	Retrospective review, ICSD-2	27/45[a]	Thirty-five males, mean age 66 y, range 29–86 y, 10 PD, 6 MCI, 5 MSA, 3 LBD, 30 OSA, 13 comorbid depression	Melatonin 6 mg per night in 25 patients, + clonazepam 0.5 mg in 2 patients, clonazepam monotherapy in 18 patients, 27.4 ± 24 months	17 (68%) improvement on melatonin, vs. 89% on clonazepam, melatonin ↓ injuries significantly	ND
Lin et al. (2013) [27]	Retrospective review, ICSD-2	28	Twenty males, 66.5 ± 9 y, 10 PD, 16 with OSA, 6 with cognitive decline	Melatonin 3–6 mg per night for 4 months, then +0.5–3 mg clonazepam	26 at 6 mg in monotherapy	Decrease of WASO and EMG bursts during total REM time
		Đ: 101			Đ: 81	

Abbreviations: *CGI* Clinical Global Impression rating scales, *LBD* Lewy body dementia, *EMG* electromyogram, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *ISCD-R/1/2* revised/first/second edition of the *International Classification of Sleep Disorders*, *MCI* mild cognitive impairment, *MSA* multiple system atrophy, *MT* movement time, *ND* not done, *NM* not mentioned, *OSA* obstructive sleep apnea, *PRBD* probable RBD, *PD* Parkinson's disease, *RCT* randomized controlled trial, *REM* rapid eye movement, *RWA* REM sleep without atonia, *vs.* versus, *VAS* visual analog scale, *WASO* wake after sleep onset, *y* years, ↑ increase, ↓ decrease, % percent

[a]Group members received several drug therapies

Table 24.2 Effects of melatonergic agonists on RBD symptoms

Author	Study type, diagnostic criteria	*N*	Patient population, concomitant diseases	Treatment, dosage, duration	*N* Responding (based on patients and bedpartners' reports)	vPSG
Bonakis et al. (2012) [28]	Case review, NM	3	iRBD	Agomelatine, 25–50 mg per night, 6 months	3 (1 at 25 mg, 2 at 50 mg)	Significant ↓of %REM epochs with high tonic density
Nomura et al. (2013) [29]	Case series, ICSD-2	2	59 y-old male, 76 y-old female, 1 PD, 1 MSA + OSA	Ramelteon 8 mg monotherapy in 1 patient, + clonazepam 1 mg in 1 patient, 2–3 y	2, 1 with rebound after discontinuation	↓in % RWA
Esaki et al. (2016) [30]	Open-labeled trial ICSD-2	12	iRBD	Ramelteon 8 mg daily, at least 4 weeks	Unclear, contradictory results, a trend toward significance on VAS	No statistically significant effect on RWA, RBD severity scale, and all other sleep parameters
Kashihara et al. (2016) [31]	Open-labeled trial ICSD-2	35	PD, sleep disorders 24 with PRBD	Ramelteon 8 mg daily, 12 weeks	Unclear, ↓scores in the Japanese RBD questionnaire	ND
		Đ: 52			Đ: unclear	

Abbreviations: see Table 24.1

were dose dependent and led to withdrawal in one patient (morning sleepiness with 9 mg melatonin and 0.5 mg clonazepam). All patients had used other psychoactive medications (donepezil, selective serotonin reuptake inhibitors (SSRI), carbi-/levodopa, psychostimulants), with no significant improvement of RBD frequency or severity. No details were given as to a possible deterioration of symptoms due to co-medication or to other co-medications such as beta-blockers.

McCarter et al. [26] retrospectively reviewed efficacy and side effects, particularly injury frequency under melatonin and clonazepam treatment among 45 patients with PSG confirmed RBD. Coexisting neurodegenerative disorders were seen in 24 patients, and almost all patients took antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRI) or SSRIs and dopaminergic and anticholinergic agents. Furthermore, 30 patients (67%) had moderate OSA, with a group median apnea-hypopnea index (AHI) of 9 (range 5–68; the authors did not report how many

of them were actually treated for OSA). Grade of severity of RBD was similar with or without neurodegenerative diseases, OSA, and concomitant medication. Twenty-five patients received melatonin, 18 received clonazepam, and 2 received both as initial treatment. The median effective dose was 6 mg for melatonin and 0.5 mg for clonazepam. Melatonin showed an overall improvement in 68% of patients, clonazepam in 89% of patients, but melatonin-treated patients reported significantly reduced injuries and fewer side effects. Efficacy of both medications was comparable, regardless of the presence or absence of comorbid neurodegenerative disorders. Eight patients switched from monotherapy with melatonin or clonazepam to a combination of both, without further improvement. The authors substantiated an association between antidepressant use and RBD frequency. Patients treated with clonazepam reported more frequent side effects than those treated with melatonin, a group difference trending toward statistical significance. Side effects associated with melatonin treatment were sleepiness (29%), trouble thinking (12%), unsteadiness (8%), nausea (8%), sexual dysfunction (8%), and dizziness (4%), each of these was most frequently rated to be mild in severity. However, the study was retrospective and had some methodological problems, so the results must be interpreted with considerable caution.

In another retrospective study, Lin et al. [27] evaluated the data from 28 patients with PSG confirmed RBD. Ten patients also showed symptoms of Parkinson's disease (PD), and four other patients exhibited cognitive decline. Patients with OSA were first successfully treated with nasal continuous positive airway pressure (CPAP). Then, all patients received melatonin, 2 patients at a dose of 3 mg nightly and 26 patients at a dose of 6 mg nightly. After 8 weeks taking a dose of 3 mg, the reports of the two patient's bed partners indicated no relevant change in extent and frequency of abnormal behaviors, nor did follow-up PSG show reduced EMG activity in REM sleep. However after 4 months treatment with 6 mg melatonin nightly, the other 26 patients showed a clear clinical improvement with significant reduction of nights with dream enactment behavior. After the first period of melatonin monotherapy, all patients began a combination therapy with clonazepam 0.5–1 mg per night. Abnormal behaviors in sleep improved but did not persist in the group with melatonin 3 mg in combination with clonazepam 0.5–1 mg nightly, so finally melatonin was increased to 6 mg. The group treated with 6 mg melatonin first and subsequently combined with clonazepam showed a significant reduction in the percent of WASO compared to baseline. The authors did not provide details to treatment-related side effects.

Only a limited number of studies have examined the efficacy of melatonergic agonists in RBD. One case series [28] described the positive effects of agomelatine in three patients with clinical and PSG confirmed idiopathic RBD (iRBD). One month after initiation of treatment with 25 mg per night, aggressive behavior had fully remitted in one patient. The other two patients, still reporting some episodes of shouting and jerking, increased the dose to 50 mg per day. This led to further improvement with clearly reduced numbers of RBD episodes by the end of the follow-up period. All patients recalled fewer dreams, and their dream content changed dramatically, turning more pleasant. After 6 months of treatment, vPSG confirmed

a trend for improved sleep efficiency and a significant decrease of REM epochs with high tonic density. Agomelatine was well tolerated and no side effects were reported.

Ramelteon has been more frequently reported in RBD therapy. Nomura et al. [29] treated two patients with symptomatic RBD with ramelteon 8 mg/night. The first patient received ramelteon in monotherapy due to contraindications for the use of clonazepam, and the other was co-administered ramelteon because of failed effectiveness with clonazepam. Both patients improved clinically, one of them completely recovered with rarely experienced dreams and with relapsing after treatment discontinuation. Side effects were not mentioned. PSG showed a decrease of RWA as well as of the AHI. An open-labeled trial with ramelteon [30] for the treatment of iRBD showed contradictory results. Twelve consecutive patients received 8 mg ramelteon daily for at least 4 weeks. The treatment did not have a clear effect on RWA or on RBD severity scale measured by vPSG, showing a significant decrease in only two patients. Furthermore, there were no statistically significant differences in all other sleep parameters. Only a visual analog scale provided by the bedpartners showed a trend toward significance. Ramelteon was well tolerated in most patients, but two patients dropped out because of side effects (drug rash, dizziness). Kashihara et al. [31] investigated the effects of ramelteon on sleep disorders, including RBD, in 35 patients with PD. The patients received 8 mg of ramelteon before sleep once daily for 12 weeks. Motor and sleep symptoms were evaluated both before and after ramelteon administration. Twenty-four of the 35 patients enrolled in this study were diagnosed with probable RBD (pRBD) using the Japanese version of the RBD screening questionnaire. Ramelteon reduced the severity of sleep disturbances in patients with PD. It also lowered scores on the Japanese version of the RBD questionnaire in patients with PD and pRBD. Unfortunately, diagnosis and treatment were not verified by PSG.

To date, no studies on the efficacy of tasimelteon for the treatment of RBD have been published.

24.4 Circadian Modulation of REM Sleep

In the discussion of the underlying mechanisms that cause the positive effects of melatonin on RBD, it is crucial to recognize that the drive for REM sleep contains the essential attributes of a circadian process, in addition to its ultradian appearance.

Under usual entrained conditions, the probability to enter REM sleep (i.e., REM sleep propensity) fluctuates systematically within 24 h, being high during the last half of the nightly sleep phase [33]. REM sleep latency depends more on circadian phase than on previous wakefulness duration [34] and shows a clear diurnal variation which suggests a circadian profile [35]. Also, while manipulating the sleep-wake cycle in the presence of a light/dark cycle, the circadian character of the REM sleep rhythm is preserved [36].

In a time cue-free environment, the crest of the circadian REM sleep propensity coincides roughly with the trough and early rising part of the body temperature

circadian rhythm, the latter representing a typical endogenous reference for circadian phase [34, 37]. This temporal relationship is preserved when the timing of the sleep-wake cycle dissociates from the circadian temperature rhythm, either spontaneously [33, 37] or with experimental protocols that force desynchrony between these variables [38, 39].

Animal research supports the notion of circadian REM sleep modulation. Attempts to enter REM sleep increased during REM sleep deprivation and were modulated by circadian phase in rats, but in SCN-lesioned animals, this circadian modulation had vanished [40]. In an elegant experiment with the crepuscular mammal *Octodon degus* diurnal and nocturnal REM sleep deprivations provoked equivalent amounts of REM sleep debts, but a consistent REM sleep rebound was found only after nocturnal deprivation, which strongly supports the notion that the circadian system actively promotes REM sleep [41].

A circadian modulation of REM sleep logically implies that next to circadian period and phase, REM sleep propensity has (circadian) amplitude and also offsets if the difference between the absolute amplitudes of minimum and maximum was unequal. In our opinion, it is first and foremost the circadian *amplitude* that represents the strength of the REM sleep propensity rhythm. This strength, in turn, would heavily depend on the timely orchestration and integrity of all processes and conditions in the circuitry that controls REM sleep.

24.5 Melatonin, Circadian Timing System, and REM Sleep

While treatment of RBD seems to be effective with exogenous melatonin and, with anecdotal evidence, also with melatonin agonists, the mode of action is still under discussion. We have assumed that this is based on the restoration of the circadian timing system integrity by stabilizing phase and amplitude of the internal clock [42]. Enhancement of the biological clock functioning by melatonin will increase the amplitude of circadian REM sleep propensity, and thus its strength, by improving the timely orchestration and integrity of all underlying processes necessary for a proper functioning of REM sleep. Improvement to a proper functioning of REM sleep might then imply alleviation of RBD symptoms.

Our hypothesis is based on a number of observations. In a randomized double-blind, placebo-controlled study with 14 patients, who were specifically selected on reduced REM sleep amounts (more than 25% below age norm), we could demonstrate that melatonin treatment significantly increased REM sleep percentage, REM sleep continuity, REM sleep polarity (i.e., short REM sleep episodes at the beginning and long REM sleep episodes at the end of the sleep period), and also the amplitude of temperature decline during nighttime sleep [43]. Although several patients in this study were non-RBD, the data demonstrate that, regardless of the underlying pathology, properly administered melatonin can normalize nighttime REM sleep and strengthen circadian amplitude.

Another relevant observation we repeatedly made is that the effects of melatonin slowly develop and clearly outlast the actual period of melatonin administration.

RBD symptoms only gradually return after the melatonin treatment is stopped, sometimes over more than a year. This observation rules out that direct "pharmacological" effects of melatonin on, e.g., body temperature or sleep consolidation would be the cause for its therapeutic effectiveness. Furthermore, we observed in our initial pilot studies with RBD patients that responders and nonresponders were best distinguished by evaluating their sleep hygiene, i.e., stable vs. varying bedtimes and times of melatonin intake [22, 43]. This clinical observation is in agreement with the fact that melatonin receptor sensitivity in the SCN varies with circadian time [44]. As a consequence exogenous melatonin should be administered consistently within a rather narrow time span in order to gain optimal effects. Both observations support our hypothesis that some kind of internal desynchrony is part of the underlying pathophysiology, implying involvement of the circadian timing system.

It might be objected that there is no identified circadian timing abnormality in RBD that has been published up to now. However, RBD may be considered as a powerful predictor, if not a prodromal marker, of neurodegenerative synucleinopathies like PD, Lewy body dementia, or multiple system atrophy, which are mostly accompanied by a substantial breakdown of the circadian system [45–47]. In this respect, disturbed circadian timing system integrity might be the link to RBD as a harbinger of neurodegenerative pathology. In our opinion, signs of circadian disruption are indeed not clearly overt in the early stages, that is, well before conversion to a full-blown synucleinopathy. Initial indications may be only very subtle and faint. But little by little, more and more elements of circadian disruption will inevitably be elucidated over the time course of conversion to synucleinopathy [46]. In our experience melatonin improves RBD symptoms in neurodegenerative disorders, but we observed complete resolution of symptoms only in those patients who had not yet converted to PD [23].

We see further hints of circadian timing system involvement when considering the growing number of reports about the melatonin receptors [44]. In particular, the hypothesized role of the MT_1 receptor in clock-related processes [6–8] and in REM sleep regulation [5, 9] seems to be of relevance. The clinical significance of the melatonin receptors in neurodegeneration is supported by histological postmortem studies. Decreased MT_1 and MT_2 receptor expression have been found in the amygdala and substantia nigra of postmortem tissue from PD patients compared to normal controls, which demonstrates a downregulation of melatonin receptors in regions affected by the disease [48].

Like clonazepam, melatonin might impact directly on REM sleep atonia via modulation of gamma-aminobutyric acid (GABA)-ergic inhibition, as proposed in a publication about a glycine/$GABA_A$-receptor knockout transgenic mouse model of RBD [49]. In PD, melatonin treatment is suggested to prevent neuronal dopamine loss and/or dopamine transporter downregulation via neuroprotective effects. It can ameliorate motor symptoms in experimental models of PD [50], and in a mouse model, it could recently be demonstrated that the loss of midbrain dopaminergic neurons leads to impairments of the circadian control of rest-activity rhythms [51].

While the interactions between SCN and melatonin-producing pineal gland are well clarified, the link between SCN and the proposed brainstem nuclei involved in

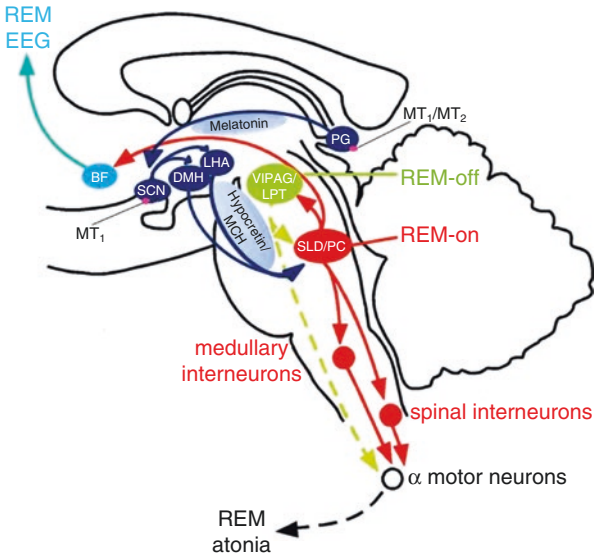

Fig. 24.1 Melatonin, circadian timing system and REM sleep in humans. Melatonin release follows a circadian rhythm and is controlled by the SCN, mainly via the MT_1 receptor, with highest levels during night, transducing the information "darkness" as a feedback signal to the SCN (blue) [2, 3]. A proposed link between circadian timing system and REM sleep controlling nuclei of the brainstem (SLD, PC) is projections of the SCN via DMH and LHA (blue) [53, 54], where MCH and hypocretin-expressing neurons participate in the regulation of neuronal activity of REM sleep [56, 57]. During REM, glutamatergic neurons in the SLD (red) activate a series of inhibitory interneurons in the medulla and spinal cord, which inhibit motor neurons, thus producing the atonia of REM sleep. Withdrawal of tonic excitatory input from the REM-off regions vlPAG/LPT (yellow, dashed lines) may also contribute to the loss of muscle tone. At the same time, ascending projections from glutamatergic neurons in the SLD and PC activate forebrain pathways (aqua) that drive electroencephalographic (EEG) desynchronization and hippocampal theta rhythms, thus producing the characteristic EEG signs of REM sleep (modified from [54]). Abbreviations: *BF* basal forebrain, *DMH/LHA* dorsomedial/lateral hypothalamic area, *EEG REM* electroencephalographic signs of REM sleep, *LPT* lateral pontine tegmentum, *MCH* melanin-concentrating hormone, *PC* pre-locus coeruleus (or subcoeruleus) area, *MT_1/MT_2* MT_1/MT_2 receptor, *PG* pineal gland, *SCN* suprachiasmatic nucleus, *SLD* sublaterodorsal tegmental nucleus, *vlPAG* ventrolateral periaqueductal gray

REM sleep control is still fragmentary. It has been shown in the rat that activity of the dorsomedial SCN (as determined by expression of PER1 gene) is associated with REM sleep propensity. This suggests that the SCN, next to gating the occurrence of sleep and wakefulness, can also shape sleep architecture by influencing the circadian sequence of specific sleep stages [52]. The SCN sends the main part of its output into the subparaventricular zone which in turn projects to the dorsomedial and lateral nucleus of the hypothalamus where MCH (melanin-concentrating hormone)-expressing neurons are active during sleep [53, 54]. Animal and in vitro studies show that acute activation of MCH neurons at the onset of REM sleep extended the duration of REM, possibly through inhibition of arousal circuits in the mammalian brain [55]. Further animal data suggest as another possible mode of action that the SCN communicates circadian phase to hypocretin-producing

cells of the dorsomedial/lateral hypothalamus via lateralized neural projections [56] whereas hypocretinergic neurons intermingled with MCHergic, and another unidentified companion group of neurons of the posterolateral hypothalamus participate in the regulation of neuronal activity in the nucleus pontis oralis, the executive site that is responsible for the generation of REM sleep in the cat [57] (summarized presentation see below in Fig. 24.1). Further research is required to gain a better insight.

Conclusions

Based on the state of knowledge, the experts of the Committee of the Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) [58] suggested both clonazepam and melatonin as Level B treatments of RBD, although to date far more cases of clonazepam therapy of RBD have been reported compared to melatonin therapy of RBD. Other drugs were rated lower, given very limited evidence. Melatonin, compared to clonazepam, has the advantage of a favorable side effect profile, whereas clonazepam should be used with caution in patients with dementia, gait disorders, or OSA.

The mode of action of melatonin and melatonergic agonists in RBD still remains unclear. We hypothesize that restoration of the circadian timing system integrity, which mainly via the MT_1 receptor subsequently promotes a stronger, proper functioning of REM sleep (and proper functioning implies flawless muscle atonia), plays an important role, although confirmation of this hypothesis awaits a substantial amount of future research. The possibly different mode of action and effectiveness of short-released and prolonged-released melatonin as well as melatonergic agonists are still an open issue.

Time of administration of melatonin and its receptor agonists seems to be important. To be most effective, melatonin should be taken shortly before the usual bedtime, at the time of increasing endogenous melatonin levels, which is between 9 and 11 p.m. in intermediate chronotypes. But even more important, it should be taken about the same time every day. Melatonergic agonists may be considered for treatment of RBD, but evidence is still limited with only a few subjects having been studied [59].

Melatonin has been reported to partially restore muscle atonia during REM sleep and was shown in our studies to have a long-lasting positive effect on both clinical symptoms and PSG findings, even after melatonin discontinuation [1, 22, 23, 43]. Adequate clinical trials with a sufficient number of cases are necessary to create evidence for a safe, effective, and reliable pharmacological treatment of RBD. A consensus statement of the International RBD Study Group [60] identified essential methodologic components for future randomized trials in RBD. The committee recommended active treatment trials of melatonin versus clonazepam for assessing comparative efficacy and side effects, considering placebo-controlled studies in RBD unethical due to the risk of major, life-threatening injuries for placebo-treated patients. Potential primary and secondary outcomes for eventual trials with disease-modifying and neuroprotective agents were also defined, considering the high conversion rate from iRBD to neurodegenerative disorders. Whereas conversion rate to synucleinopathy in clonazepam-treated RBD patients

is high [61, 62], no comparable data are available yet for melatonin-treated RBD patients. In our opinion, the conversion rate in RBD patients, comparing clonazepam with melatonin, will be a most fascinating aspect of proposed upcoming trials, with proper randomization being critical. Early recognition of RBD and its effective treatment may lengthen the symptom-free period in the early phase of developing neurodegenerative disorders [63, 64].

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