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Themed Section: Recent Developments in Research of Melatonin and its Potential Therapeutic Applications

REVIEW ARTICLE

New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation

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In mammals, a central circadian clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, tunes the innate circadian physiological rhythms to the ambient 24 h light–dark cycle to invigorate and optimize the internal temporal order. The SCN-activated, light-inhibited production of melatonin conveys the message of darkness to the clock and induces night-state physiological functions, for example, sleep/wake blood pressure and metabolism. Clinically meaningful effects of melatonin treatment have been demonstrated in placebo-controlled trials in humans, particularly in disorders associated with diminished or misaligned melatonin rhythms, for example, circadian rhythm-related sleep disorders, jet lag and shift work, insomnia in children with neurodevelopmental disorders, poor (non-restorative) sleep quality, non-dipping nocturnal blood pressure (nocturnal hypertension) and Alzheimer's disease (AD). The diminished production of melatonin at the very early stages of AD, the role of melatonin in the restorative value of sleep (perceived sleep quality) and its sleep-anticipating effects resulting in attenuated activation of certain brain networks are gaining a new perspective as the role of poor sleep quality in the build-up of β amyloid, particularly in the precuneus, is unravelled. As a result of the recently discovered relationship between circadian clock, sleep and neurodegeneration, new prospects of using melatonin for early intervention, to promote healthy physical and mental ageing, are of prime interest in view of the emerging link to the aetiology of Alzheimer's disease.

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Abbreviations

AD, Alzheimer's disease; Aβ, Amyloid-β; DMN, default mode network; DSPS, delayed sleep phase syndrome; IR, immediate release; MCI, mild cognitive impairment; N24HSWD, non-24 h sleep–wake disorder; NREM, non-rapid eye movement; PRM, prolonged-release melatonin; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SWS, slow wave sleep

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Introduction

Daily cycles in physiology and behaviour appear to be a universal feature of living organisms, from single cells to humans, resulting in profound periodic changes in physiological and behavioural conditions between states of high and low activity during the 24 h day–night cycle. In mammals, including humans, the circadian system is organized into a hierarchical manner with a central pacemaker in the suprachiasmatic nucleus (SCN) of the brain's hypothalamus (Levi and Schibler, 2007). The SCN synchronizes the circadian physiological and behavioural rhythms, including sleep and wakefulness, temperature, feeding, neuroendocrine and autonomic effects, with the 24 h periodicity to match the environmental light–dark cycle, thereby orchestrating an optimized internal temporal order. Light is the primary stimulus for tuning (entraining) the SCN rhythm period and phase with the external environment. The SCN has direct connections to other hypothalamic nuclei (Deurveilher *et al.,* 2002). This multistage processor provides the organism with flexibility so that environmental cues, such as food availability, ambient temperature and social interactions, can be integrated with the clock signal to sculpt an adaptive pattern of rhythmic daily activities (Saper *et al.,* 2005). A neural output signal, generated by the SCN, induces the synthesis of **melatonin** at night by the pineal gland. The hormone is released into the third ventricle and subsequently the circulation (Reiter, 1991). Light, in addition to tuning the SCN, acts to inhibits melatonin synthesis. Because melatonin is metabolized rapidly, plasma melatonin levels are low during the day and high during the night. The dim light melatonin onset, which is the initial surge in melatonin release in the early part of the night under low light conditions, is a consistent and reliable measure of the intrinsic circadian phase (Lewy, 1999).

The sleep–wake cycle is the most overt circadian rhythm. Sleep is an orchestrated neurochemical process involving sleep-promoting and arousal centres in the brain (Saper *et al.,* 2005). Sleep has a major role in the restoration of brain energy, in the switching off of external inputs and off-line processing of information acquired during wake, in the facilitation of the plasticity of cerebral changes that underlie learning, memory consolidation and extinction, and in the activation of the recently discovered glymphatic system that is responsible for brain metabolite clearance (Musiek and Holtzman, 2016). These functions are critical for brain development, physical and mental health, and the maintenance of cognitive functions culminating in a sense of well-being and daytime vigilance.

Based on characteristic polysomnography signals, sleep has been divided into two distinct states known as rapid eye movement (REM) and non-rapid eye movement (NREM) that alternate in a periodic manner throughout the night. NREM sleep characterized by the presence of a minimum of 20% high voltage low frequency cortical δ waves (ranging from 0.5–2 Hz known as NREM 3) is also termed slow wave sleep (SWS) or deep sleep and provides an indication of the intensity or depth of sleep. Sleep propensity depends on the amount of sleep deprivation (homeostatic component) and on time of day (circadian clock component). The interaction between these processes forms the basis of a remarkably standardized bout of sleep at night and a consolidated bout of wakefulness throughout the day (reviewed in Zisapel, 2007). The duration of wakefulness predicts the amount of SWS regardless of the circadian phase. The circadian component of the sleep propensity function is presumably regulated by the SCN *via* indirect innervation of the sleep promoting centre, which resides in the ventrolateral preoptic nucleus (Deurveilher *et al.,* 2002).

Melatonin is an important physiological sleep regulator in diurnal species including humans. The sharp increase in sleep propensity at night usually occurs 2 h after the onset of endogenous melatonin production in humans (Lavie, 1997; Zisapel, 2007); in addition, the duration of nocturnal melatonin relays night length information to the brain and various organs, including the SCN itself. The circadian melatonin rhythm is closely associated with the sleep rhythm in both normal and blind subjects (Zisapel, 2001). Ageing, the presence of certain diseases [e.g. primary degeneration of the autonomic nervous system and diabetic neuropathy, some types of neoplasms and Alzheimer's disease (AD)] and certain drugs (e.g. β-blockers, clonidine, naloxone and non-steroidal anti-inflammatory drugs) abolish the nocturnal production of melatonin and are associated with impaired sleep. Administration of melatonin during daytime (when it is not present endogenously) results in the induction of fatigue and sleepiness in humans (Gorfine *et al.,* 2006). Importantly, melatonin is not sedating: in nocturnally-active animals, melatonin is associated with awake, not sleep, periods and in humans, its sleep-promoting effects become significant about 2 h after intake similar to the physiological sequence at night (Zisapel, 2007). The effects of exogenous melatonin can be best demonstrated when endogenous melatonin levels are low (e.g. during daytime or in individuals who produce insufficient amounts of melatonin) and are less recognizable when there is a sufficient rise in endogenous melatonin (Haimov *et al.,* 1994; Kunz *et al.,* 1999; Tordjman *et al.,* 2013).

In humans and other diurnal species, melatonin acts at the SCN to attenuate the wake-promoting signal of the circadian clock, thus promoting sleep (Liu *et al.,* 1997). In addition, melatonin acts at the default mode network (DMN) regions in the brain to promote fatigue and sleep-like changes in activation of the precuneus (Gorfine *et al.,* 2006; Gorfine and Zisapel, 2009). The DMN is a network of brain regions that is active during rest in the absence of task-dependent performance (Raichle *et al.,* 2001). It consists of the medial prefrontal cortex, posterior cingulate cortex and precuneus, inferior parietal lobe, lateral temporal cortex and hippocampal formation and is involved with interoceptive awareness and mind wandering (Spreng *et al.,* 2010). Within this network the precuneus is involved in a variety of complex functions, which include recollection and memory, integration of information (gestalt) relating to perception of the environment, cue reactivity, mental imagery strategies, episodic memory retrieval and affective responses to pain (Cavanna and Trimble, 2006). While asleep, connectivity within the DMN decreases and is diminished during SWS (Horovitz *et al.,* 2009). Melatonin given in the afternoon to healthy young individuals attenuates activation in the precuneus, located at the rostro-medial aspect of the occipital cortex (Figure 1A). These effects correlate with subjective measurements of fatigue (Gorfine *et al.,* 2006). However, activation

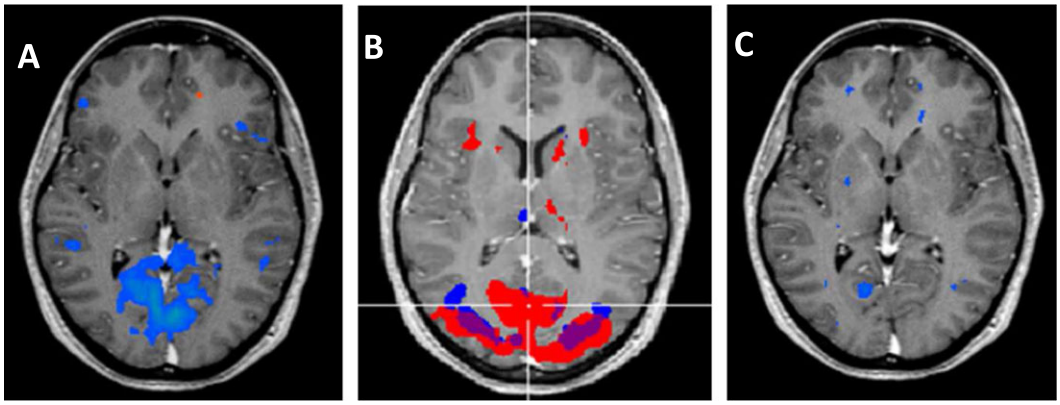

Figure 1

The fMRI-assessed visual search task related activation of brain networks (adapted from Gorfine *et al.,* 2006; Gorfine and Zisapel, 2009). (A) The effect of exogenous melatonin administration at 16:00 h on task-related activity. In a double-blind, crossover design with 10 days between treatments, subjects had a baseline and a randomized treatment fMRI session, commencing 1 h later. The drugs (melatonin 2 mg in 100 mL of 1% ethanol in water or placebo 100 mL of 1% ethanol in water) were given p.o. after the baseline session and subjects were instructed to remain awake in ambient room light for 1 h to allow the ingested melatonin to reach maximal levels in the blood. Drug effect was defined by a conjunction analysis of two contrasts: activation after melatonin intake > activation before melatonin intake and activation after melatonin intake > activation after placebo intake. This analysis identifies regions that are affected by melatonin while excluding changes resulting from placebo or second examination effects. The image depicts the statistical parametric map of melatonin versus placebo effect analysis (conjunction analysis, $P < 0.05$ uncorrected). Blue indicates decreased activation following melatonin but not placebo intake. (B) The experiment was repeated as described in (A) with exogenous melatonin administration at 22:00 h. To evaluate time of day effects on brain activity, group activation maps were generated for the baseline fMRI scans of the 14 subjects from the night trial and the 12 subjects of the reference (afternoon) trial. Brain areas demonstrating significant task-related activity at 16:00 h but not 22:00 h were identified. The image depicts statistical parametric maps ($P < 0.01$ corrected) demonstrating task-related activation at 16:00 h (red) and 22:00 h (blue). Purple denotes overlapped activation. The crossing white lines denote the precuneus area. (C) The effect of exogenous melatonin administration at 22:00 h on task-related activity. The experiment was repeated as described in (A) with exogenous melatonin administration at 22:00 h. Drug effect was defined by a conjunction analysis of two contrasts: activation after melatonin intake > activation before melatonin intake and activation after melatonin intake > activation after placebo intake. This analysis identifies regions that are affected by melatonin while excluding changes resulting from placebo or second examination effects. The image depicts the statistical parametric map of melatonin versus placebo effect analysis (conjunction analysis, $P < 0.05$ uncorrected) showing no difference in activation of the precuneus following melatonin and placebo intake.

of this brain area is decreased concomitantly with the endogenous rise of melatonin, so that administration of exogenous melatonin at night does not have a further notable effect (Figure 1B,C). Because melatonin does not increase the amount of SWS (Arbon *et al.,* 2015), which is considered a marker of the homeostatic sleep pressure (Zisapel, 2007), the sleep promoting effects of melatonin may be mostly ascribed to the circadian component of sleep regulation.

The role of melatonin in the regulation of the circadian clock and sleep has led to translational research into melatonin as a treatment of human disease, in particular circadian rhythm and sleep disorders, with further implications as a disease modifying agent in neurodegenerative and cardiovascular disease as described below.

Melatonin in the treatment of circadian rhythm and sleep disorders in humans: clinical evidence

Circadian rhythm sleep disorders

Melatonin serves as a time cue (signal of darkness) to various organs including the SCN itself and in the absence of light, may entrain the sleep–wake and neuroendocrine rhythms to the 24 h cycle (reviewed in Zisapel, 2001). Totally blind subjects frequently report severe, periodic sleep problems, with 50–75% of cases displaying non-24 h sleep–wake disorder (N24HSWD) due to an inability to synchronize with the environmental day–night cycle (Emens and Eastman, 2017).

Melatonin therapy is a rational approach for N24HSWD in the totally blind population (Zisapel, 2007; Emens and Eastman, 2017). The administration of immediate release (IR) melatonin to totally blind individuals with N24HSWD (0.5–10 mg, once daily in the evening for 1 day up to several months) facilitated phase advances and entrainment to the societal sleep/wake norms and reportedly entrained endogenous melatonin and cortisol rhythms to the 24 h cycle. Recent studies suggest that modified release preparations can be effective for phase stabilization in totally blind N24HSWD patients (Roth *et al.,* 2015). A **melatonin receptor** agonist, **tasimelteon**, was recently approved by the USA-FDA for the treatment of N24HSWD in the blind (Dhillon and Clarke, 2014).

In other circadian rhythm sleep disorders [e.g. delayed sleep phase syndrome (DSPS) and advanced sleep phase syndrome (ASPS)], the individual's circadian rhythm of sleep and wakefulness is entrained to 24 h but out of phase with the conventional environmental patterns. DSPS is characterized by sleep-onset insomnia and difficulty in awakening at the desired time, and ASPS is characterized by early sleep onset and early awakening. Disorders associated with jet lag and shift work are due to temporary misalignment of the

circadian sleep–wake rhythm with environmental patterns (Zisapel, 2001).

The pathophysiological process of circadian rhythm sleep disorders is presumed to be associated with the pacemakers, their coupling to the external cues, or their downstream synchronizing mechanisms (reviewed in Zisapel, 2001; 2007). In DSPS the endogenous melatonin rhythms are delayed compared with those in normal individuals. There is compelling evidence indicating that melatonin effectively advances sleep onset and wake times of subjects with DSPS to earlier hours compared to placebo and improved vigilance and cognitive functions in these patients. Although not approved for this indication, melatonin is rigorously used for phase shifting following trans-meridian flights in healthy individuals. Approval of the melatonin receptor agonist tasimelteon for N24HSWD in the blind provides compelling evidence of the utility of melatonin receptor agonists for disorders related to clock phase resetting (Emens and Eastman, 2017).

Sleep disorders

Insomnia in adult subjects. Insomnia is a pervasive disorder characterized by difficulties in initiating or maintaining sleep or non-refreshing sleep (also termed non-restorative or poor quality sleep) for at least 1 month and is associated with clinically significant daytime distress or impairment in social, occupational or other important areas of functioning. In primary insomnia, the disorder has an unknown physical, mental or environmental cause (APA, 2008; WHO, 2008). Non-restorative sleep (subjectively perceived poor sleep quality) is a distinct pathology which might occur independently of difficulties falling asleep or poor sleep maintenance (Roth *et al.,* 2010). Daytime impairment in insomnia may include, but is not limited to, problems such as fatigue, memory impairment, mood disturbances, proneness for errors, tension headaches and gastrointestinal symptoms in response to sleep loss (Edinger *et al.,* 2004).

Several studies have shown that insomnia characterized by poor sleep quality and insufficient quantity of sleep are associated with impaired daytime functioning (e.g. negative effects on memory, vigilance and psychomotor skills) physical health problems, anxiety, depression and fatigue, higher cardiovascular risk and poor quality of life (Zeitlhofer *et al.,* 2000; Hoevenaar-Blom *et al.,* 2011). This association identifies the quantitative and qualitative aspects of sleep as being essential for the restoration of body and mind. Poor quality (non-restorative) sleep seems to be an important type of insomnia among the elderly population (Buysse *et al.,* 1989; Edinger *et al.,* 2004).

The production of melatonin generally decreases with age (Waldhauser *et al.,* 1998; Kunz *et al.,* 1999). Older subjects show an increased lag from sunset to the onset of melatonin pulse and to the melatonin pulse peak and between melatonin secretion peak and the middle of the sleep period. The apparent relationship between increasing age, declining melatonin production and increasing insomnia prevalence has led to the 'melatonin replacement' hypothesis, which suggests that replenishing the deficiency in the endogenous sleep-regulating hormone will improve sleep. Attaining physiological control of the sleep/wake cycle is the aim of melatonin replacement therapy in children with neurodevelopmental disorders as it is also in insomnia patients aged 55 and older, because these groups tend to have low endogenous melatonin production throughout the night (Haimov *et al.,* 1994; Tordjman *et al.,* 2013).

A meta-analysis of controlled human intervention studies in normal sleepers and subjects with primary insomnia indicated a statistically significant reduction of sleep onset latency following immediate release (IR) melatonin consumption (Buscemi *et al.,* 2005; Zisapel, 2012). Melatonin did not improve any other aspects of sleep quantity.

Melatonin is absorbed rapidly following oral administration and undergoes first-pass hepatic metabolism with peak plasma levels occurring between 20 min and 2 h, and levels persist for up to 1.5 h, depending on the dose, before declining at a half-life of about 40 min (Zisapel, 2010; Figure 2). Treatment of disorders that are associated with diminished nocturnal melatonin secretion may require a formulation that would reproduce the normal nocturnal pattern of melatonin secretion and provide effective melatonin levels throughout the night (Figure 2). Placebo-controlled clinical

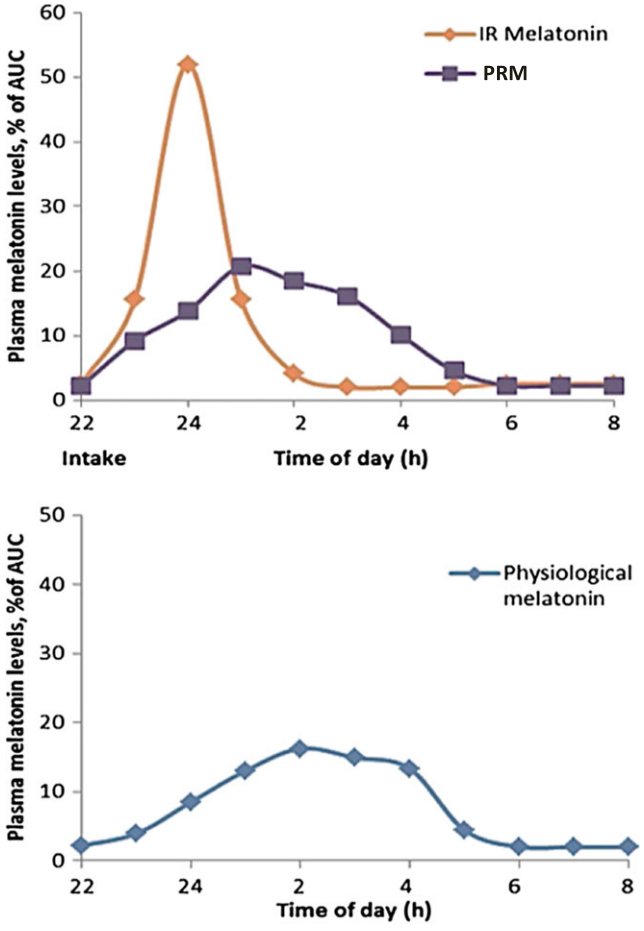

Figure 2

Mean plasma levels of ingested (A) and endogenous (B) melatonin. (A) Pharmacokinetics of prolonged-release (PRM) versus immediate-release (IR) melatonin 2 mg formulations. Results are mean plasma melatonin levels following drug intake and expressed as % of the AUC (adapted from Zisapel, 2010). (B) Mean endogenous plasma melatonin levels (adapted from Zhdanova *et al.,* 1998).

trials using an adequately defined prolonged-release melatonin (PRM) formulation, specifically addressing the efficacy and safety of melatonin replacement therapy for insomnia in patients aged 55 and older (Lemoine and Zisapel, 2012), have demonstrated that PRM improves subjectively-perceived sleep quality as well as shortening sleep latency and, most importantly, improves morning alertness and quality of life suggesting improvement in the restorative quality of sleep. These and more recent studies show that PRM preserves physiological sleep structure, does not cause amnesia or increase the risk of falls that are typically associated with traditional hypnotics and is safe for short-term and long-term use in older people, even in the presence of the most frequent comorbidities (e.g. hypertension, diabetes, cardiovascular disease and AD) and concomitant medications for these comorbidities. Based on the clinical evidence, PRM was approved in the EU and many other countries and recommended as a first-line treatment for insomnia characterized by poor sleep quality (non-restorative sleep) in patients aged 55 and older (Wilson *et al.,* 2010). Interestingly, efficacy increases with time reaching a plateau after 13 weeks and thereafter (Zisapel, 2012). Decreased melatonin **MT_1** receptor expression has been reported in the suprachiasmatic nucleus in ageing (Wu *et al.,* 2007). It has yet to be elucidated whether the build-up of efficacy represents up-regulation of MT_1 receptors in the SCN and other brain areas, thereby increasing sensitivity to melatonin or whether it represents synchronization of the internal temporal order (Dubocovich, 2007).

Sleep disturbances in children with autism spectrum disorder and neurogenetic neurodevelopmental disorders. Paediatric insomnia is a widespread problem with prevalence of 1–6% in the general paediatric population and 50–75% in children with neurodevelopmental or psychiatric comorbidities, specifically autism spectrum disorder (ASD; including autistic disorder, Asperger's disorders and pervasive developmental disorder) and neurogenetic disorders (NGD, e.g. Rett's disorder, tuberous sclerosis, Smith–Magenis syndrome and Angelman syndrome) (Kotagal and Broomall, 2012; Elrod and Hood, 2015). The sleep disturbances exacerbate cognitive performance deficits and behavioural problems and subsequently entire family distress (Doo and Wing, 2006). A growing body of evidence indicates abnormal melatonin secretion and circadian rhythmicity in children with neurodevelopmental disorders, specifically ASD, which may explain the abnormal development of sleep/wake cycles, noted since the first year of life; such abnormalities justify the use of melatonin for insomnia in these populations (De Leersnyder, 2006; Tordjman *et al.,* 2013). The use of melatonin for treating chronic sleep–wake cycle disorders of children with ASD/NGD is increasing (Rossignol and Frye, 2011; Cortesi *et al.,* 2012; Gringras *et al.,* 2012; 2017; Malow *et al.,* 2012; Cuomo *et al.,* 2017). In a recent meta-synthesis of published studies on the effectiveness of sleep-based interventions for children with ASD, it was concluded that melatonin, behavioural interventions and parent education/interventions appear the most effective at ameliorating multiple domains of sleep problems (Cuomo *et al.,* 2017). Melatonin-based therapy, if approved by the health authorities, could become a standard treatment of insomnia in neurodevelopmentally-challenged children.

Potential disease modifying properties in sleep-related aspects of neurodegenerative and cardiovascular disease

Nocturnal dipping in blood pressure rhythms. Approximately 40% of the 55+ population report insomnia and an overall dissatisfaction with quality of sleep (Weyerer and Dilling, 1991) and approximately 30% of the age 55+ population have hypertension (Hull *et al.,* 2011). A bidirectional link exists between insomnia and hypertension; 43% of insomnia patients have hypertension, compared to 19% among good sleepers; 44% of hypertensive patients have insomnia, compared to 19% among normotensive patients (Thase, 2005; Taylor *et al.,* 2007; Roth, 2009; Hoevenaar-Blom *et al.,* 2011). Nocturnal hypertension is significantly higher in older than younger patients (63.1 vs. 41.1%). BP falls during sleep and rises rapidly just before the time of awakening. The circadian rhythm in BP, characterized by a 10–20% decline in BP during sleep time, is essential for cardiovascular health (Hermida *et al.,* 2010; 2013). Failure to reduce BP during the night ('non-dipping') is associated with a 1.5–3.3 higher risk of developing cardiovascular disease compared to dippers (Hermida *et al.,* 2010; 2012; Grandner *et al.,* 2012). The prevalence of non-dipping was significantly higher in older than younger patients (63.1 vs. 41.1%) (Hermida *et al.,* 2013).

A 10–15 year follow-up study on 20 432 men and women aged 20–65 years with no history of cardiovascular disease in the Netherlands (the MORGEN study) showed that poor sleep quality even more than quantity, increased the risk of cardiovascular disease and coronary heart disease (Hoevenaar-Blom *et al.,* 2011). Decreased SWS is associated with a 1.8-fold increased risk of developing hypertension in elderly men (Fung *et al.,* 2011). The circadian rhythm of BP is blunted in patients with insomnia, even in those who are normotensive (Lanfranchi *et al.,* 2009). Inversely, non-dippers have poor quality of sleep (Pedulla *et al.,* 1995).

Diminished melatonin production at night has consistently been reported in severely hypertensive patients and non-dippers (Jonas *et al.,* 2003; Zeman *et al.,* 2005) and in the elderly and in patients with coronary diseases (Brugger *et al.,* 1995). Thus, a melatonin deficiency alone or associated poor sleep quality may be causally related to an impaired nocturnal BP fall. Night-time PRM reduced BP in untreated male patients with essential hypertension and significantly reduced nocturnal systolic BP in patients with nocturnal hypertension treated with anti-hypertensive drugs (Grossman *et al.,* 2011). There is less compelling evidence for this effect with IR melatonin preparations (Grossman *et al.,* 2011). The most significant effect of the PRM was between 02:00 and 06:00 h, a time when BP is rising in non-dippers, compatible with the prolonged action of this formulation. The 6 mmHg reduction in mean systolic BP overnight and 4.2 mmHg in the diastolic BP in the melatonin- versus placebo-treated group is clinically meaningful because a decrease of 5 mmHg in mean asleep-systolic BP or 2.1 mmHg in diastolic BP could potentially save 1585 cardiovascular events per 100 000 patient-years (Hermida *et al.,* 2010).

Importantly, melatonin improves sleep in hypertensive patients with sleep disorders (Lemoine *et al.,* 2012; Scheer *et al.,* 2012). Unlike current hypnotics of the benzodiazepine and non-benzodiazepine (Z-drugs) class, melatonin preserves physiological sleep structure and architecture and does not suppress SWS (Zisapel, 2012; Arbon *et al.,* 2015). Through its activity on sleep and the circadian clock, add-on PRM to anti-hypertensive therapy can potentially improve clinical outcome in hypertensive patients with insomnia. Whether melatonin add-on therapy can improve cardiovascular outcome with ageing remains to be further explored.

Rapid eye movement sleep behaviour disorder (RBD). RBD is a sleep disorder characterized by loss of muscle atonia (i.e. the loss of paralysis) during REM sleep allowing patients to act out their dreams. RBD is often the first indication of an impending α-synuclein disorder, such as Parkinson's disease, multiple-system atrophy, or dementia with Lewy bodies (Howell and Schenck, 2015). There is emerging evidence that treatment with melatonin effectively improves the clinical and neurophysiological aspects of RBD, especially elderly individuals with underlying neurodegenerative disorders (Kunz and Mahlberg, 2010). Because RBD is a prodromal syndrome of Parkinson's disease (or related disorders), it represents a unique opportunity for testing the disease-modifying potential of melatonin therapy.

Sleep and circadian rhythm regulation in cognitive functioning and Alzheimer's disease. Sleep represents a biological condition most appropriate for consolidating memories (Diekelmann and Born, 2010). In healthy humans, periods of sleep following learning consistently enhanced retention of the learned material in a variety of memory tasks compared to wakefulness. Considering the role of sleep in memory consolidation, it is not surprising that insufficient sleep can reduce cognitive ability including attention and memory. These symptoms are of particular concern in older subjects, because they may be misinterpreted as symptoms of dementia/mild cognitive impairment (MCI) (Roth and Ancoli-Israel, 1999). There is a strong association of objectively and subjectively measured sleep quality with subsequent cognitive decline (Osorio *et al.,* 2011; Blackwell *et al.,* 2014).

AD is a progressive neurodegenerative brain disorder that accounts for 60–70% cases of dementia in the ageing population. Classical hallmarks of AD are insoluble extracellular senile plaques composed of the **β amyloid** (Aβ) peptide and intracellular tangles comprising hyperphosphorylated τ aggregates (Perrin *et al.,* 2009). Aβ plaques accumulate in the brains of AD patients' years before the onset of cognitive impairment and serve as an early biomarker of AD (Ju *et al.,* 2013).

Mechanisms linking circadian clocks, sleep and neurodegeneration have recently been demonstrated (Musiek and Holtzman, 2016). The presence of insomnia is significantly associated with AD [odds ratio (OR) = 3.32, 95% CI = 1.33–8.28] (Osorio *et al.,* 2011). Poor sleep quality is more frequent in MCI and AD patients compared to age-matched good sleepers (Hita-Yanez *et al.,* 2012) and as many as 63% of patients with MCI, and 44% of patients with AD demonstrate sleep disturbance. The presence of sleep disorders increases the risk of future cognitive decline in normal older adults (Osorio *et al.,* 2011; Lim *et al.,* 2013) and faster cognitive deterioration in AD patients, suggesting a bi-directional relationship between sleep and AD (Miyata *et al.,* 2013; Spira and Gottesman, 2017). Sleep disruption, especially the reduction in SWS and or increased wakefulness may suppress the function of the glymphatic system that could result in a decreased clearance of pathogenic proteins such as Aβ, which in turn may result in Aβ accumulation and the development of the symptoms of Alzheimer's disease (Musiek and Holtzman, 2016).

Functional hippocampal–neocortical (regions within the DMN) connectivity is imperative for memory consolidation and retrieval (Diekelmann and Born, 2010). While asleep, connectivity within the DMN decreases and is diminished during SWS (Horovitz *et al.,* 2009). It was suggested that poor sleep quality results in an increase in DMN connectivity during sleep and subsequently increased neuronal activity and, therefore, Aβ production and release. Indeed, the DMN areas are most susceptible to Aβ plaque formation in AD. PET studies of the link between β-amyloid deposition and self-reported sleep in older adults have shown, after adjustment for potential confounders, that a shorter sleep duration is associated with greater Aβ burden in cortical areas and the precuneus. Lower sleep quality was associated with greater Aβ burden in the precuneus (Spira *et al.,* 2013). Importantly, Aβ overlaps DMN regions in which hypometabolism and atrophy were detected in AD patients (Buckner *et al.,* 2005). Aβ deposition in the preclinical stage of AD appears to be associated with worse sleep quality (Ju *et al.,* 2013; Spira and Gottesman, 2017) and was also associated with worse cognitive and memory performance (Molano *et al.,* 2017). An alternative mechanism linking sleep and Aβ has been recently suggested (Mendelsohn and Larrick, 2013), whereby sleep can facilitate the removal of toxic proteins and other molecules from the brain through regulation of the 'glymphatic' system (Jessen *et al.,* 2015). Extracellular Aβ is vacated by this mechanism twice as fast as during NREM SWS than during awake periods (Xie *et al.,* 2013). If a causal link exists between the accumulation of Aβ in DMN regions and neurodegeneration in AD, interventions that improve sleep among older adults may ameliorate Aβ burden and slow down the sleep-related AD onset and progression (Figure 3) (Landry and Liu-Ambrose, 2014; Lucey and Bateman, 2014; Musiek *et al.,* 2015).

Early neuropathological changes in preclinical AD stages are accompanied by decreased levels of melatonin (Tohgi *et al.,* 1992) and correlated significantly with the severity of mental and sleep impairments in demented patients (Mishima *et al.,* 1999). The loss of melatonin may exacerbate the disruption of the sleep–wake rhythm, and exogenously administered melatonin may in principle mitigate the loss and improve the restorative value of sleep. A recent Cochrane review article concluded that there is no evidence that treatment with IR melatonin, at doses up to 10 mg over 8 to 10 weeks, resulted in statistically significant differences in objective sleep measures (assessed by actigraphy) compared to a placebo in patients with AD who were identified as having a sleep disturbance (McCleery *et al.,* 2016). As explained above, the restorative value of sleep (subjectively perceived sleep quality) not necessarily sleep quantity may be more relevant for older subjects. A multicentre, randomized trial of 10 mg

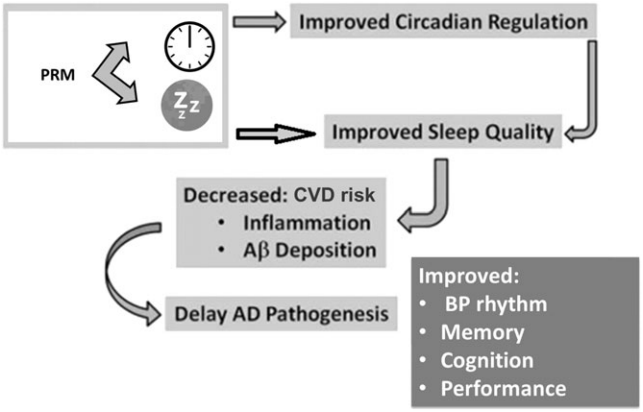

Figure 3

Proposed effects of melatonin on mechanisms linking circadian clocks, sleep and neurodegeneration in AD (adapted from Landry and Liu-Ambrose, 2014; Musiek and Holtzman, 2016). Sleep–wake and circadian disruption may precede neurodegeneration and the development of cognitive symptoms. The sleep–wake cycle appears to regulate levels of the pathogenic amyloid-β peptide in the brain, blood pressure rhythms and inflammation. Improving sleep and the circadian clock functioning can influence these processes, reduce cardiovascular risk, inflammation and amyloid-β accumulation and thereby slow down the neurodegenerative process. Melatonin, through its beneficial effects on the circadian clock functions and sleep–wake cycle, may delay AD-related pathology.

IR melatonin, 2.5 mg slow-release melatonin (of undisclosed pharmacokinetics, not PRM), or placebo in subjects with AD and night-time sleep disturbance has shown that while melatonin did not significantly differ from placebo in objective sleep measures, caregiver ratings of sleep quality showed improvement in the 2.5 mg slow-release melatonin group relative to placebo (Singer *et al.,* 2003). A long-term (6 months) study of PRM 2 mg versus placebo in mild/moderate AD patients showed benefits of PRM versus placebo in maintaining or improving cognitive functioning (Wade *et al.,* 2014). Thus, add-on PRM to standard therapy improved memory and cognition in the patients as assessed by the "AD Assessment Scale – cognition, Mini Mental State examination" and attenuated the decline in task performance as assessed by "Instrumental Activities of Daily Living". The results also suggested a statistically significant improvement in subjectively-assessed sleep efficiency compared to placebo, although not all patients had a diagnosis of insomnia. Treatment effects were independent of adjunctive memantine treatment and effect sizes were greater in the Insomnia AD subpopulation (Wade *et al.,* 2014). As in older patients with insomnia, the effect on sleep evolved during 13 weeks of treatment to reach a plateau that was maintained throughout the rest of the 6 months study period. Alterations in melatonin receptor expression (decrease in MT_1 receptors in the suprachiasmatic nucleus, pineal and cortical brain areas and up-regulation in the hippocampus and decrease in **MT_2** receptors in the hippocampus, pineal and cortical areas) have been reported in AD (Savaskan *et al.,* 2005; Brunner *et al.,* 2006; Wu *et al.,* 2007). Whether the build-up of efficacy in AD patients represents a reinstatement of MT_1/MT_2 receptors that are lost in AD or a reinforcement of their circadian rhythmicity is still unknown. The effects of melatonin treatment in MCI and early AD remain to be explored.

The ability of melatonin to improve the restorative value of sleep, through its effects on the circadian clock and reduced activation of the precuneus, open new perspectives into the role of clock and sleep disturbances in the pathophysiology of AD. The relationship between these effects, attenuated Aβ overproduction and enhanced clearance of accumulated amyloid to decrease Aβ load in this region, warrant further investigation.

Concluding remarks

Melatonin, the hormone produced by the pineal gland at night, serves as a time cue to the biological clock and promotes sleep anticipation in the brain default mode network (DMN); these effects may explain the increase in sleep propensity in circadian rhythm sleep disorders and the enhanced restorative sleep in older patients with insomnia. With age and certain diseases, the robustness of the circadian system decreases and melatonin production is diminished or shifted. Deviant circadian rhythms and poor sleep quality are associated with increased risks of cardiovascular, metabolic and cognitive diseases, poor quality of life and mortality. Exogenously administered melatonin improves non-restorative sleep and circadian rhythm amplitudes and misalignments. The ability of melatonin to reduce activation of the DMN (precuneus) may explain the enhancement of the restorative value of sleep (sleep quality) in insomnia patients, and its beneficial effects on cardiovascular health and cognitive decline in patients with AD. The ability of exogenously administered melatonin to mitigate the loss of the endogenous night signal and improve the restorative value of sleep represents a promising investigational route for early intervention to promote healthy physical and mental ageing.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.,* 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.,* 2017).

Conflict of interest

N.Z. is the founder and Chief Scientific Officer of Neurim Pharmaceuticals, the company that developed and produces prolonged release melatonin-Circadin®.

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