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Chronophysiology of Melatonin: Therapeutical Implications

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Abstract: Normal circadian rhythms are synchronized to a regular 24 hr environmental light/dark cycle. Both the suprachiasmatic nucleus (SCN) and melatonin are essential for this adaptation. Melatonin exerts its chronophysiological action in part by acting through specific receptors (MT_1, MT_2) which have been identified in the plasma membrane of SCN as well as in several neural and non-neural tissues. Both receptors have been cloned and share general features with other G protein linked receptors. Melatonin also exerts direct effects on intracellular proteins such as calmodulin or tubulin and has strong free radical scavenger properties which are non-receptor mediated. Within the SCN, melatonin reduces neuronal activity in a time-dependent manner. SCN MT_1 and MT_2 receptors appear to be insensitive during the day, but sensitive at dusk and dawn (MT_2; causes phase shifts) or during early night period (MT_1; decreases neuronal firing rate). Melatonin secreted during nighttime provides enough inertia to resist minor perturbations of the circadian timing system. The disruption of these circadian mechanisms cause a number of sleep disorders named according to the International Classification of Sleep Disorders as circadian rhythm sleep disorders (CRSDs). CRSDs include delayed or advanced sleep phase syndromes, non 24 hr sleep/wake rhythm disorder, time zone change syndrome ("jet lag") and shift work sleep disorder. Disturbances in the circadian phase position of plasma melatonin levels have been found in all these disorders. In addition, co-morbility of severe circadian alterations with neurodegenerative diseases like Alzheimer´disease (AD) has been documented. Although further research involving larger number of patients suffering CRSDs is required, currently there is sufficient evidence to implicate endogenous melatonin as an important mediator in CRSD pathophysiology. Melatonin and its analogs can constitute useful therapeutic tools to treat disturbed sleep-wake rhythms in CRSDs. Melatonin secretion decreases in AD patients and its administration improves sleep efficiency, sundowning and cognitive function. This effect can be particularly important in mild cognitive impairment, an etiologically heterogeneous syndrome characterized by cognitive impairment preceding dementia.

Keywords: Circadian rhythms, suprachiasmatic nucleus, melatonin receptors, circadian rhythm sleep disorders;, Alzheimer´disease, mild cognitive impairment.

INTRODUCTION

The objective of this review article is to discuss some aspects of melatonin chronophysiology including the manner in which the circadian system regulates melatonin and the sleep-wake cycle, the ways in which melatonin interacts with the circadian system and the sleep-wake cycle and studies on the use of melatonin or its analogs to treat Circadian Rhythm Sleep disorders (CSRDs) as well as the circadian alterations seen in Alzheimer´disease (AD).

CRSDs have become a major focus of attention in recent years [1]. Major industrial, air and train accidents have been generally attributed to inefficient handling of situations by individuals suffering from fatigue due to a malfunctioning circadian time keeping system [2]. Also contributing to industrial accidents is the scheduling of the work itself. There is evidence that job performance is negatively impacted by night shift work, especially when the hours of work include the period when melatonin is normally at its peak of production (the "circadian trough") [3]. The resulting decrements in alertness and performance are further exacerbated by poor quality sleep, another condition which often afflicts night shift workers. These effects are frequently cited as the principal cause of industrial accidents occurring during non-daytime hours. Similarly affected are long distance truck drivers and others who must do extended highway driving. It has been found that sleep-related motor vehicle accidents are about twenty times greater at 0600 h than at 1000 h [4].

Synchronization of the sleep/wake rhythm and the rest/activity cycles with the light/dark (LD) cycle of the external environment is essential for maintaining man's normal mental and physical health. The hormone melatonin, which is produced mainly in the pineal gland, is essential for this physiological adaptation This is particularly apparent in pathological conditions such as CRSDs, which are known to result from disturbances to the rhythm of melatonin secretion [5,6]. The remission of CRSD symptoms following the normalization of melatonin's secretion cycle is further evidence of the central role played by chronobiological factors in these disorders [7].

The melatonin secretion cycle represents a convenient means for observing the body's circadian time keeping system [8]. Since a disruption in the rhythm of melatonin secretion is a central feature of CRSDs, an increasing amount of evidence now shows that the strategic application exogenous melatonin itself can be of benefit in resynchronizing the altered circadian pattern [7,9,10].

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In AD patients melatonin secretion decreases and exogenous melatonin administration improves sleep efficiency, sundowning and, to some extent, cognitive function [11]. This effect can be particularly important in mild cognitive impairment (MCI), an etiologically heterogeneous syndrome characterized by cognitive impairment preceding dementia. Approximately 12% of MCI patients convert to AD or other dementia disorders every year [12]. Recent studies indicate that melatonin can be a useful add-on drug for treating MCI in a clinical setting [13].

CIRCADIAN RHYTHMS AND THEIR REGULATION

Genomic self-sustained oscillators have become recognized as "biological clocks" which regulate core processes in the body. A series of transcription-translation feedback loops comprising both positive and negative elements (clock genes) is at the core of the biological clock. During the past decade, considerable progress has been made in determining the molecular components of the biological clock [14]. The system provides output signals that are capable of regulating the expression of other, clock-controlled, genes [15]. Indeed, mutations of clock genes affect diverse parameters of the circadian system, including amplitude, period and phase (or, in some extreme cases, render the system completely arrhythmic). It is interesting that some of these mutations have a profound effect on human behavior [16,17].

Circadian timing provides temporal organization of most biochemical, physiological and neurobehavioral events in a manner beneficial to the organism [18]. This is the basis of a predictive homeostasis that allows the organism to anticipate events for an optimal adaptation. For example, every day and prior to waking, plasma cortisol, sympathetic tone and body temperature rise, anticipatory to increased activity and postural change.

Although anchored genetically, circadian rhythms are synchronized (entrained) by and maintain certain phase relationships to exogenous factors (environmental time cues or Zeitgebers), especially the sleep portion of LD schedule. The rhythms will persist with a period slightly different from 24 h when external time cues are suppressed or removed, such as when the organism is in complete social isolation or subjected to constant light or darkness [14].

There is a hierarchy of pacemakers with the hypothalamic suprachiasmatic nucleus (SCN) as the master pacemaker. The SCN comprises a small group of hypothalamic nerve cells that coordinates timing of the sleep-wake cycle as well as coordinating it with circadian rhythms in other parts of the brain and peripheral tissues [19] (Fig. **2**). The SCN consists of a set of individual oscillators that are coupled to form a pacemaker. Anatomically the SCN in the rat comprises two major subdivisions, a core and a shell [20]. The core lies adjacent to the optic chiasm, comprises predominantly neurons producing vasoactive intestinal polypeptide or gastrin-releasing peptide colocalized with gamma-aminobutyric acid (GABA) and receives dense visual inputs from the retino-hypothalamic tract (RHT) and geniculothalamic tract (GHT) as well as midbrain raphe afferents. It contains a population of non-rhythmic cells that are responsive to light [21]. In contrast the shell surrounds the core, contains a large population of arginine vasopressin - producing neurons in its dorsomedial portion, and a smaller population of calretinin -producing neurons dorsally and laterally, colocalized with GABA, and largely receives input from non-visual hypothalamic, brainstem and medial forebrain regions. However, there is overlap in cell populations and functions between these anatomical regions [20,21]. In the absence of periodic environmental synchronizers the circadian pacemaker is free running with a period very near to 24 hours in mammals. In humans the interindividual differences are small, however, a large scale epidemiologic study showed that differences in sleep-wake times show a near Gaussian distribution with extreme cases at each end; extreme early cases woke as extreme late ones fell asleep [22].

Without constant adjustment of the circadian pacemaker the body's endogenous rhythms can be phase delayed by up to an hour each day and consequently have a significant impact on overall health [23]. Abnormal phase positions, which are prominent features of circadian rhythm disorders, can severely desynchronize the pattern of sleeping and waking, as well as other circadian rhythms [1,24-29]. These sleep disorders are named according to the International Classification of Sleep Disorders as circadian rhythm sleep disorders (CRSDs) (Fig. **1**). CRSDs include delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), non 24 hr sleep/wake rhythm disorder, time zone change syndrome ("jet lag") and shift work sleep disorder. Disturbances in the circadian phase position of plasma melatonin levels have been found in all these disorders.

Genetic screening has shown that polymorphisms in human clock genes are correlated with alterations in sleep or diurnal preferences [16]. For example, in DSPS a correlation with certain polymorphisms in the clock gene hPer3 has been demonstrated [30] while a mutation in the hPer2 gene is associated with familiar ASPS [31]. CRSDs respond better to chronobiological manipulations involving, e.g., the use of phototherapy or melatonin, rather than to conventional hypnotic therapy [32-34]. Melatonin's ability to readjust disturbed circadian rhythms to their correct phase position [35] has increasingly led to its use in clinical applications as a chronobiotic agent [6,36,37].

MELATONIN SYNTHESIS AND CIRCADIAN EFFECTS

Melatonin is the primary hormonal output of the circadian system. Its synthesis as well as other circadian rhythms is controlled by a circadian signal from the SCN. The photoperiod is the major entraining influence on the SCN with inputs arriving from the retina via the RHT and the GHT (Fig. **2**).

Partially originating from a subset of directly photosensitive retinal ganglion cells that contain the recently discovered photopigment of entrainment, melanopsin [38], the neurotransmitters participating in the RHT are glutamate and the pituitary adenylyl cyclase-activating peptide, both released at the SCN level [39,40]. The action spectrum for melatonin suppression in man is in keeping with a shortwave non-rod, non-cone photopigment [41] . Moreover it has been shown that alerting effects of light are most pronounced at very short (420-460 nm) wavelengths [42]. Retinal projections to the intergeniculate leaflet of the lateral geniculate complex subsequently project to the SCN via the GHT [19]. Light
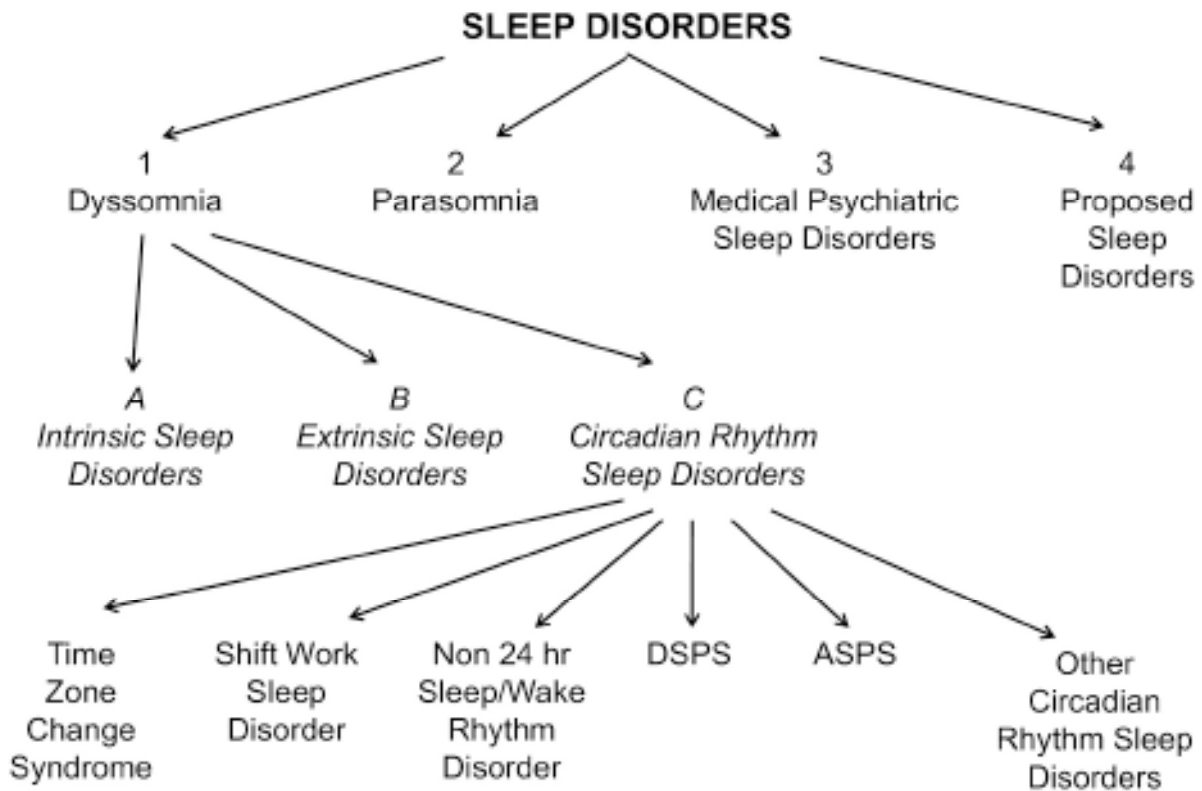
SLEEP DISORDERS

Fig. (1). Circadian rhythm sleep disorders as a type of dyssomnia according to the International Classification of Sleep Disorders. DSPS: delayed phase sleep disorder; APSD: advanced phase sleep disorder.

acts via these tracts to entrain the rhythm in the SCN as well as acting downstream of the SCN clock to block the activity of the pineal gland.

Regulation of circadian rhythms is via diverging pathways. Output from the SCN is limited; major efferents go caudally to the subparaventricular zone (SPZ) and dorsomedial nucleus, dorsally to the midline thalamus and rostrally to the anterior hypothalamus and preoptic area [43,44]; a minor projection goes to the paraventricular nucleus (PVN) (Fig. **2**).
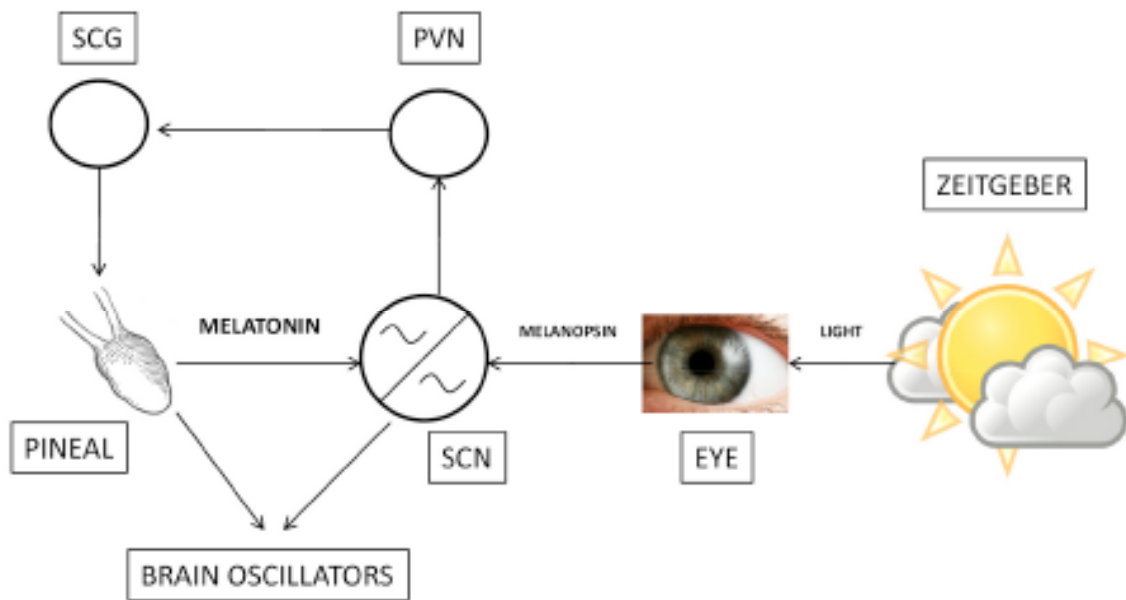
The SCN acts on the pineal gland via a complex multisynaptic pathway. Although circadian synthesis of melatonin is controlled by the SCN, light also acts downstream of the SCN overriding the circadian signal to block activity of the pineal gland. The SCN projects to the autonomic subdivision of the PVN of the hypothalamus which in turn projects directly to the upper thoracic intermediolateral cell column. Preganglionic sympathetic noradrenergic fibers project to the superior cervical ganglion which send postganglionic sympathetic noradrenergic fibers to the pineal gland to stimulate synthesis of melatonin [45].

Norepinephrine released from the sympathetic fibers acts on the pineal via a dual receptor mechanism. It activates adenylyl cyclase via β_1-adrenergic receptors [46] and protein kinase C activity via α_{1B}-adrenergic receptors [47], which potentiate β_1-adrenergic receptor activation of adenylyl cyclase. There is therefore a very rapid, large increase in cyclic 3',5'-adenosine monophosphate which leads to phosphorylation of the enzyme arylalkylamine N-acetyltransferase (AANAT). When phosphorylated, AANAT is activated by formation of a reversible regulatory complex with 14-3-3 proteins [48]. AANAT, the enzyme that converts serotonin to N-acetylserotonin, has a pivotal role in the timing of melatonin synthesis. It increases speedily with a doubling time of about 15 min in response to darkness onset and in response to light it shows an even more rapid half life of degradation of 3.5 min [48]. Since melatonin itself has a half life in the circulation of about 30 min in man, its levels change rapidly in response to circadian signals and light [49,50].

Hydroxyindole-O-methyltransferase (HIOMT), the enzyme that catalyzes production of melatonin from N-acetylserotonin, appears to be responsible for the amplitude of the nocturnal peak of melatonin [51,52]. By using a combination of molecular approaches together with a sensitive in-vivo measurement of pineal indoles it was shown that N-acetylserotonin is present in vast excess during the night allowing the conclusion that although AANAT is the rhythm-generating enzyme it is not rate limiting for nocturnal production [53]. HIOMT activity in the rat is regulated both by a short term non-adrenergic stimulus and by a longer term adrenergic stimulus [54].

Once formed, melatonin is not stored in the pineal gland but is immediately secreted into the bloodstream. In plasma melatonin binds mostly to albumin [55]. It then passes through the choroid plexus to the cerebrospinal fluid [56]. Endogenous melatonin, whether measured in saliva or in urine, is often referred to as a "hormonal finger print", having a profile which is both unique and yet consistently predictable (on a daily and weekly basis) within the individual [57]. This differs from the high interindividual variability of circulating melatonin levels, presumably of a genetic origin

Fig. (2). Light impinging on the eye send neural signals to the SCN via a group of retinal ganglion cells that contain melanopsin as a photopigment. The SCN in turn acting via a complex indirect pathway sends a circadian signal to the pineal gland regulating synthesis of melatonin as well as to other brain sites to regulate brain oscillators. Melatonin feeds back on the SCN as well as affects numerous brain and peripheral sites that contain melatonin receptors. PVN: paraventricular nucleus

[58]. In humans, plasma melatonin begins to increase steadily after 1900 to 2300 h and reaches its peak value between 0200 to 0400 h [59]. The levels then decline, reaching their lowest values during daytime hours. The rhythm is well preserved from childhood to adulthood but after approximately the age of 55 the nocturnal peak of melatonin production begins to decline, a possible contributing factor to insomnia which is often seen among the elderly [60].

The first attempts to identify brain melatonin receptors employed ^{3}H-melatonin as a radioligand to label binding sites in membranes from bovine hypothalamus, cerebral cortex, and cerebellum [61]. This was followed by the discovery of the first functional melatonin receptor in a neuronal mammalian tissue, the rabbit retina [62,63]. In 1984, Vakkuri *et al.* [64] introduced the radioligand 2- ^{125}I-iodomelatonin as a tracer for use in melatonin radioimmunoassays. This molecule turned out to be the silver bullet of melatonin receptor research as its selectivity and high specific activity allowed the field to move forward. By using this ligand, binding sites for melatonin were identified in a wide variety of central and peripheral tissues [65,66]. Molecular cloning of the first high affinity melatonin receptor (MT_1) by Reppert and coworkers [67] was accomplished using a cDNA library constructed from a dermal cell line of melanophores, the first tissue in which melatonin's action had been demonstrated. This initial finding led to the discovery that there is another G_i-protein coupled melatonin receptor in humans. The second receptor (MT_2) [68] is 60% identical in amino acid sequence to the MT_1 receptor. Yet a third receptor, now called GPR50, shares 45% of the amino acid sequence with MT_1 and MT_2 but does not bind melatonin [69]. It is unusual in that it lacks N-linked glycosylation sites and that it has a C-terminal that is over 300 amino acids long.

A fourth 2- ^{125}I-iodomelatonin binding site was identified in mammals [70] (MT_3, initially called ML-2). Unlike the picomolar membrane receptors it is a nanomolar binding site with a specific pharmacologic profile and fast kinetics of association/ dissociation [71]. It has now been purified from hamster kidney and characterized as the analog of quinone reductase type 2 [72].

A combination of reagents derived from the molecular clones and pharmacologic tools have revealed a considerable amount of information about the MT_1 and MT_2 receptors [73]. For example it has been shown that the MT_1 receptor inhibits firing acutely in SCN slices, and that both MT_1 and MT_2 may contribute to phase shifting in these slices [74]. MT_1 and MT_2 have also been shown to differentially regulate $GABA_A$ receptor function in SCN [75].

Recently it has been shown that many G protein-coupled receptors (GPCR), including the MT_1 and MT_2 receptors, exist in living cells as dimers. The relative propensity of the MT_1 homodimer and MT_1/MT_2 heterodimer formation are similar whereas that of the MT_2 homodimer is 3-4 fold lower [76,77]. It is of considerable interest that the GPR 50 receptor, though lacking the ability to bind melatonin, abolishes high affinity binding of the MT_1 receptor through heterodimerization [78,79]. Thus the GPR50 receptor may have a role in melatonin function by altering binding to the MT_1 receptor.

Mapping of the MT_1 and MT_2 receptors in brain though not yet complete has revealed much information. As expected, MT_1 and MT_2 receptors are present in the SCN [80]. They are also found in several other brain areas and in the periphery. The MT_1 receptor is extremely widely distributed in the hypothalamus: of particular note it is colocalized with corticotrophin in the PVN and with oxytocin and vasopressin in the PVN and supraoptic nucleus [80]. MT_1 receptors are

found in the cerebellum>= occipital cortex>= parietal cortex> temporal cortex> thalamus> frontal cortex >= hippocampus [81]. MT_2 receptors have been identified in the hippocampus [82], MT_1 plus MT_2 in the occipital cortex [83] and MT_1 in the dopaminergic system [84].

Melatonin is the prototype of a class of drugs that influence the circadian apparatus and are referred to as chronobiotics [32,36,37,85]. The response to melatonin follows a phase response curve (PRC), so that morning administration causes a delay, while evening administration causes an advance on circadian rhythms [86]. This PRC is about 12 h out of phase with the PRC to light which causes a phase advance in the morning and a phase delay in the evening [87]. A recent detailed PRC for melatonin (3 mg) established that the maximum advance portion peaked about 5 h before DMLO in the afternoon, the maximum delay portion was about 11 h after DMLO shortly after habitual awakening and a dead zone was in the first half of usual sleep [88]. Maximum advance and delay shifts were 1.8 and 1.5 h, respectively.

In a study of one hour sleep schedule advance combined with both early morning light and afternoon melatonin treatment (0.5 or 3 mg) it was shown that the addition of melatonin caused a significantly greater phase advance of 2.5 h, again with minimal side effects [89]. There was no difference between the two melatonin doses. Thus effects of morning light and evening melatonin are additive and can be used to cause pre-adaptation prior to eastward flight [90].

MELATONIN AND THE REGULATION OF THE SLEEP-WAKE CYCLE

Sleep can be defined as a natural state characterized by a reduction in voluntary motor activity, a decreased response to stimulation (i.e., increased arousal threshold), and stereotypic posture which is easily reversible [91]. It has been proposed that the sleep-wake cycle can be explained by a two process model; one a homeostatic drive for sleep (Process S) and the second a circadian rhythm of alertness (Process C) [92,93]. The drive for sleep is thought to be due to the accumulation of a sleep promoting substance (currently unknown) during waking. This factor increases during waking but is counteracted by an increasing circadian drive for arousal until evening when the drive for arousal decreases and the sleep factor predominates. The abrupt increase in sleep propensity is attributed to the impending melatonin increase in blood which inhibits SCN neural activity and suppresses the circadian drive [94].

The waking state is characterized by high frequency low amplitude electrical activity in the electroencephalograph (EEG) in the 14- to 30-Hz range (beta waves); this state is maintained by multiple neural inputs from the ascending reticular activating system via diverse routes to the thalamus and cortex [19,43]. Of these inputs only the upper midbrain reticular formation and posterior hypothalamus inputs appear to be essential.

Use of the EEG has shown that sleep is divided into stages without rapid eye movement (NREM) and with rapid eye movement (REM), the latter stage being associated with dreaming [95]. The sleep EEG alternates periodically between five stages, one which is accompanied by REM and four which show no REM. NREM and REM sleep alternates with a period of approximately 90 minutes. The transition of

wake to sleep is typically to slow wave sleep. It is accompanied by increased firing of a small nucleus in the preoptic area: the ventrolateral preoptic nucleus (VLPO) which projects GABA neurons that inhibit the areas aroused by the ascending reticular activating system [43]. Interaction between the VLPO and components of the arousal systems has been shown to be mutually inhibitory, and thus these pathways function analogously to an electronic "flip-flop" switch/circuit [91]. Such a flip-flop switch is inherently stable in either end state but avoids intermediate states.

Control of the sleep-wake cycle is via caudal afferents from the SCN [44,91]. The principal neuronal output pathway that determines the timing of circadian behavior: the rest-activity, sleep-wake cycle, feeding and adrenal steroid secretion is mediated by a primary projection from the SCN to the ventral SPZ, followed by a secondary projection to the dorsomedial hypothalamus. This area sends a dense glutamatergic projection to the lateral hypothalamus (overlapping with the field of orexin containing neurons) and an intense GABAergic projection to the VLPO. Control of the temperature rhythm is via a projection to the dorsal SPZ. These pathways to the SPZ from the SCN differ from those for the control of melatonin which project to the PVN (Fig. **2**).

MELATONIN AND DELAYED SLEEP PHASE SYNDROME

DSPS is mainly encountered in young individuals [96,97]. A common sleep/wake disorder that accounts for 10 % of insomniacs who are diagnosed in sleep laboratory , DSPS is due to altered physiological timing in the biological clock [98]. In this condition the timing of sleep onset and wake time are delayed [99]. The onset of sleep is delayed in some cases to 0200 – 0600 h. Neither sleep architecture nor the maintenance of sleep is affected [99,100]. However, persons suffering from this disorder experience chronic sleep onset insomnia and forced early awakening results in daytime sleepiness. It has been shown that the peak melatonin secretion occurs between 0800 h and 1500 h in some DSPS patients demonstrating the abnormal phase position of melatonin in this sleep disorder [99].

DSPS is the most frequently occurring CRSD [1,101]. Dagan and Eisenstein [97] found that 83.5 % of 322 CRSD patients were of the DSPS type. The prevalence of DSPS in adolescence is more than 7 % [102-104]. Among those with DSPS an onset of symptoms which occurred in early childhood was reported by 64.3 % of the sample, in the beginning of puberty by 25.3 %, and during adulthood by 10.4 % [97]. Even a minor brain injury or a head trauma can act as a trigger for the development of DSPS, [105,106] . DSPS can also follow whiplash injury [107]. Frequently occurring jet lag or frequently occurring shift-work are also risk factors for the development of DSPS [99,108]. Regestein and Monk reported that 75 % of their patients had a prior history of depression [100]. DSPS persists even after remission of the depression thus suggesting that DSPS may be a cause rather than a consequence of depression. There is evidence that symptoms of chronic fatigue with late melatonin onset can occur following a viral infection [109,110]. Fluvoxamine use has also been reported as a trigger for DSPS [111] .

Because of its effectiveness in resetting the biological clock, exogenous melatonin therapy has attracted research

interest for its applicability for treating DSPS. Dahlitz and co-workers were the first to report a placebo-controlled study that demonstrated the efficacy of melatonin in the treatment of DSPS patients [112,113]. A 5 mg dose of melatonin was administered orally at 2200 h to patients suffering from DSPS for a period of 4 weeks. In those studies, it was noted that melatonin significantly advanced the sleep onset time by an average of 82 min, with a range of 19 to 124 min. The mean wakefulness time also advanced by 117 min [112,113]. Though the total duration of sleep remained unaltered (mean about 8 h) after melatonin treatment, there was a significant improvement in sleep quality.

For maximum treatment effectiveness the timing of administration is just as critical for melatonin administration as it is for the application of bright light therapy [114]. Lewy *et al.* [86] found that when melatonin was administered 5 h before endogenous melatonin onset, it advanced circadian time maximally. Therefore Nagtegaal *et al.* [115] administered melatonin 5 h before the onset of the evening rise of endogenous melatonin secretion (the 'dim-light melatonin onset', or DLMO) for a period of 4 weeks and found phase advancement in the sleep/wake rhythm. The onset of the nocturnal melatonin profile was found to be phase advanced by 1.5 h. Following this report, Kayumov *et al.* [116] administered melatonin to a group of 22 patients with DSPS who had their sleep time restricted to the 8 h period between 2400 h and 0800 h. Melatonin in a dose of 5 mg/day was administered 3 to 4 h before sleep onset for a period of 4 weeks. Melatonin significantly phase-advanced the sleep period, and decreased sleep onset latency as compared to placebo [116]. No adverse effects of melatonin were noted. In addition it was found that exogenous melatonin normalized the circadian pattern of melatonin excretion in three of the five patients who had an abnormal melatonin production showing a peak melatonin excretion between 0800 and 15.00 h. Melatonin was also shown in placebo-controlled studies to be effective for treating children with idiopathic chronic sleep onset insomnia, which is related to child onset DSPS [117,118].

MELATONIN AND ADVANCED SLEEP PHASE SYNDROME

The changes in sleep patterns which occur with advancing age can, in part, be attributed to changes in the functioning of the circadian oscillator [119-121]. The characteristic pattern of ASPS includes complaints of persistent early evening sleep onset and early morning awakenings [122,123]. Typically in ASPS, sleep onset occurs at around 2000 h and wakefulness occurs at around 0300 h [124]. The quality of sleep is progressively impaired by increased awakenings occurring during the night [125]. It has been suggested that this impairment is due to an attenuation of the rhythm of melatonin secretion which in turn may disrupt the phase relationships of the sleep/wake cycle as well as other circadian rhythms [126] .

Leger *et al.* [127] in studies undertaken in 517 human subjects aged 55 years and above noted a significant decline in the secretion of 6-sulfatoxymelatonin, the principal urinary melatonin metabolite, in subjects suffering from insomnia. Among the affected subjects the output of 6-sulfatoxymelatonin averaged 9.0 microgram/night, compared to 18.0 microgram/night for other subjects of the same age group. Melatonin replacement therapy was administered in dosages of 2 mg of controlled release tablets (Circadin™), and was found to improve significantly the sleep quality of patients in the insomnia group [127]. Also affected were measures of alertness and behavioral integrity, which also showed improvements in these subjects. These findings were interpreted to support the conclusion that decrements in sleep quality, which are often seen among the elderly, are largely attributable to a decline in the production of melatonin, which also occurs with advancing age. The evidence was also taken to support the conclusion that melatonin promotes sleep possibly through circadian entraining effects as well as by a sleep-regulating effect.

Genetic testing has provided support for the conclusion that ASPS is also an inherited sleep-wake rhythm disorder with an autosomal dominant mode of inheritance [16]. Indeed, alteration in the function of clock genes has been documented as one of the major causes of CRSDs.

MELATONIN AND TIME ZONE CHANGE SYNDROME (JET LAG)

Rapid transmeridian flight across several time zones results in a temporary mismatch between the endogenous circadian rhythms and the new environmental LD cycle [128]. As a result endogenous rhythms shift in the direction of the flight; an eastbound flight will result in a phase advance of rhythms while a westbound flight will produce a phase delay [9]. The re-establishment normal phase relationships differs from one rhythm to another. Because of this phenomenon a transient desynchronization of circadian rhythms occurs, giving rise to a cluster of symptoms. These symptoms typically include transiently altered sleep patterns (e.g., disturbed night time sleep, impaired daytime alertness and performance), mood and cognitive performance (e.g. irritability and distress), appetite (e.g. anorexia), along with other physical symptoms such as disorientation, fatigue, gastrointestinal disturbances and light-headedness that are collectively referred to as "jet lag" [128,129].

There have been a number of field studies on melatonin given close to bedtime as a treatment for jet lag on eastward flights as reported in recent reviews [130,131]. In most but not all studies report a reduction of jet lag symptoms. One negative study [132] involved participants who flew from Norway to New York and returned home on fifth day after taking melatonin. They would not have been fully acclimatized to New York and thus had an inappropriate baseline. The other study [133] reported an initial improvement after three days of melatonin with no continuing improvement but the analysis is unclear. Furthermore this study involved crossing eastward over ten times zones and the timing of initial administration was at the wrong position of the PRC for melatonin. Several studies reported an improved quality and duration of sleep [134-138] or accelerated resynchronization of rhythms [139,140]. Doses used in these studies ranged from 0.5 to 10 mg, with more soporific effect with doses of 5 or 10 mg and little difference in phase response between doses. Melatonin at bedtime on eastbound flight provides benefits from both the soporific and phase resetting effects. Studies using melatonin on westbound flights have been few and have revealed less benefit than after eastbound

flight [139,141,142]. An exception is a study [143] using a combination of 3 mg bed time melatonin with exercise and light exposure in two- three hour time blocks (08:00 to 11:00 and 13:00 to 16:00) for six days at the destination after 12 h westward flight in athletes. Although this study lacked a placebo control, resynchronization was reported after 2.13 days, much more rapidly than would be expected. Use of light in this manner is theorized to cause blunting or masking of the endogenous circadian signal and sensitization to Zeitgebers [144]. In a follow-up study that again used 3 mg melatonin at bedtime in combination with only 30 min or more of outdoor exercise in the same two time blocks it was reported that after westward travel of 11 h resynchronization occurred in 2.54 days while after 13 h eastward travel it occurred in 2.27 days [37]. Although there was no placebo control, adaptation to the new environment occurred much more rapidly than would be expected. These studies provide strong support for the use of combined strategies for treatment of jet lag. Controlled field studies of such combined treatments would yield evidence-based advice to be provided for travelers.

MELATONIN AND SHIFT WORK SLEEP DISORDER

It has been estimated that in our modern industrialized society at least one fifth of total work force is engaged in rotating shift work [145,146]. These individuals are forced to forego their nocturnal sleep while they are on a nightshift, and sleep during the day. This inversion of the sleep/wake rhythm with work at night at the low phase of the circadian temperature rhythm and sleep at the time of peak body temperature has given rise to insomnia-like sleep disturbances. Sleep loss impairs the individual's alertness and performance that affects not only work productivity but also has been found to be a major cause for industrial and sleep related motor vehicle crashes [147]. Sleep related crashes occur most commonly in the early morning hours (0200-0600 h) [148]. Sleep deprivation and the associated desynchronization of circadian rhythms are common in shift-work sleep disorder [146].

Many treatment procedures have been advocated. Czeisler and co-workers administered bright light for improving the physiological adaptation of the circadian rhythms of night-shift workers to their inverted sleep/wake schedules [149]. In this study bright light was found effective for re-synchronizing alertness, cognition, performance, and body temperature to the new work schedules. Following the successful application of bright light, melatonin has been used in shift workers to accelerate adaptation of their circadian rhythms and sleep/wake rhythms to the new work schedules (see, e.g [150,151]). A phase delay in plasma melatonin was noted in shift workers when melatonin was administered at the morning bedtime following the night shift [152]. The shift in melatonin secretion has been associated with increase in work performance as well [153]. Correctly timed administration of melatonin is advocated for hastening adaptation of circadian rhythms in shift-workers, inasmuch as melatonin administration in the evening (1600 h) does not affect daytime sleepiness and mood [154]. Rajaratnam *et al.* have recommended the use of melatonin in situations such as shift work in which there is a misalignment of the circadian clock to external time cues [155,156]. Melatonin (1.5 mg at 1600h) was found to advance the timing of both endogenous melatonin and cortisol rhythms without causing any deleterious effects on endocrine function or daytime mood and sleepiness [154]. There is evidence that combination of both bright light and melatonin can be an effective and reliable strategy for treating shift work disorder.

MELATONIN AND NON 24-HOUR SLEEP/WAKE DISORDER

Non 24-hour sleep/wake disorder is seen mostly in blind human subjects since their sleep/wake cycle is not synchronized to the 24-hour LD cycle. These subjects suffer from recurrent insomnia and daytime sleepiness. The circadian rhythm of sleepiness has shifted out of phase with the desired time for sleeping [157]. Melatonin has been employed to correct right abnormal sleep/wake rhythms in blind human subjects [158]. In two studies melatonin treatment has been found to completely synchronize the sleep/wake cycle of blind human subjects to a 24-hour cycle [159,160]. Lockley *et al.* used 5 mg of melatonin to phase advance and normalize the rhythms of three totally blind persons [159]. Sack and his co-workers administered 10 mg of melatonin for 3 to 9 weeks to 7 totally blind persons and found that melatonin was effective in inducing phase-advances of sleep/wake rhythms by 0.6 h/day [160]. On reaching complete entrainment, the dose was gradually reduced and synchronization of sleep/wake rhythms to the normal 24 hr day schedule was maintained with a low dose of 0.5 mg that resulted in plasma melatonin concentrations close to the physiological range [160]. In this study the authors were able to show that the beneficial effects of melatonin could be attributed not only to its entrainment properties but also to its direct soporific effects. The findings that at close to physiologic concentrations melatonin is capable of maintaining and/or resynchronizing circadian sleep/wake rhythms supports the view that melatonin is an important part of human circadian system.

The prevalence of non-24-hour sleep/wake rhythm disorder among sighted patients is unknown, but it is believed to be rare. Fewer than 50 cases have been reported in the world literature, and of these the vast majority have been from Japanese publications [161-163]. Only 9 cases have been documented outside of Japan and these have been predominantly male and associated with avoidant or schizoid personalities [164-168]. Thus, non 24-hour sleep/wake disorder is a rare sleep disorder among sighted patients in Western populations. Only 3 patients were seen over a span of about 20 years in a sleep clinic that services a yearly average of over 500 patients, a small percentage of which are circadian rhythm disorders (Dr. L. Kayumov, personal communication). In the Japanese population it has been estimated that non-24-hour sleep/wake rhythm disorder comprises 23 % of all CRSDs [101]. The prevalence of circadian rhythm disorders in this population (0.13 - 0.4 %) is consistent with that observed in other populations [104].

It is likely that this sleep disorder is rare in Western populations because it is under-diagnosed. Diagnosis is complicated by the fact that at times non-24-hour sleep/wake rhythm disorder can resemble both ASPS and DSPS and in fact exhibit the same polysomnographic features. A recently completed polysomnographic study was performed on 22 untreated DSPS patients [116]. During imposed sleep periods (from 2400 to 0800 h) the patients generally showed delayed sleep onset latencies (averaging 1 hour), abnormal

distribution of SWS across the night (with the greatest amount of deep sleep in the early morning hours), short sleep duration (less than 6 hours) and an increased amount of intervening wakefulness. The patients with non-24-hour sleep/wake rhythm disorder displayed almost identical polysomnographic features since the baseline recordings were performed during delayed phases of their cycles [116]. The fact that exogenous melatonin entrained the sleep cycles of the patients strongly suggests that the primary defect is a failure of the circadian clock to entrain normally to the environmental LD cycle. Patients with non-24-hour sleep/wake rhythm disorder demonstrate a psychiatric co-morbidity, such as depression, which may result from years of living out of synchrony with the rest of society.

Under certain circumstances, irregular CRSD may arise. For example, treatment with psychotropic drugs such as haloperidol [24] can trigger a CRSD of an irregular type. In addition, prolactin secreting microadenomas [169] , or occupational inadequate exposure to bright light can be related to the development of irregular CRSD [170]. Minor head trauma can cause irregular CRSD as well as DSPS [106]. Most of reports of this type of CRSD refer it to the influence of environmental and medical conditions.

MELATONIN AND CIRCADIAN RHYTHM ABNORMALITIES IN ALZHEIMER´S DISEASE

AD is an age-associated neurodegenerative disease that is characterized by a progressive loss of cognitive function, loss of memory, and several neurobehavioral manifestations. Concomitantly melatonin levels are lower in AD patients compared to age-matched control subjects. Decreased CSF melatonin levels observed in AD patients reflect a decrease in pineal melatonin production rather than a diluting effect of CSF. CSF melatonin levels decrease even in preclinical stages when the patients do not manifest any cognitive impairment (at Braak stages I-II), suggesting that the reduction in CSF melatonin may be an early marker for the first stages of AD [171]. The reduction in nocturnal melatonin levels with the abolition of diurnal melatonin rhythmicity may be the consequence of dysfunction of noradrenergic regulation and depletion of the melatonin precursor serotonin by increased monoamine oxidase A activity, as already seen in the earliest preclinical AD stages. Alternately, changes in the pathways of light transmission, from physical properties of the dioptric apparatus to a defective RTH- or SCN-pineal connections have been discussed as possible reasons of declines in melatonin amplitude and corresponding changes in the circadian system [172]. The changes in melatonin secretion could contribute to some frequent symptoms like sleep disruption, nightly restlessness and sundowning seen in AD patients [173].

AD patients with disturbed sleep-wake rhythms did not only exhibit reduced amounts of melatonin secreted, but also a higher degree of irregularities in the melatonin pattern, such as variations in phasing of the peak [174,175]. Therefore, the melatonin rhythm has not only lost signal strength in clock resetting, but also reliability as an internal synchronizing time cue. Loss or damage of neurons in the hypothalamic SCN and other parts of the circadian timing system may account for the circadian rhythm abnormalities seen in demented patients, especially as the number of neurons in the SCN of AD patients is reduced [11].

In both elderly subjects and in patients suffering from dementias the administration of exogenous melatonin has been found to not only to enhance sleep quality but also to improve the sleep/wake rhythm in clinical setting studies [173,176-179]. In a double-blind study, the major findings with regard to melatonin effects on sleep-wake rhythmicity, cognitive and non-cognitive functions were confirmed [180].

In a multicenter, randomized, placebo-controlled clinical trial, two dose formulations of oral melatonin were applied: 157 subjects with AD and nighttime sleep disturbance were randomly assigned to 1 of 3 treatment groups: (i) placebo, (ii) 2.5 mg slow-release melatonin, or (iii) 10 mg melatonin given daily for 2 months [181]. In this study, a statistical problem became apparent, since melatonin facilitated sleep in a certain number of individuals, but collectively the increase in nocturnal total sleep time and decreased wake after sleep onset, as determined on an actigraphic basis, were only apparent as trends in the melatonin-treated groups. On subjective measures, however, caregiver ratings of sleep quality showed significant improvement in the 2.5 mg sustained-release melatonin group relative to placebo [181]. Large interindividual differences between patients suffering from a neurodegenerative disease are not uncommon. It should be also taken into account that melatonin, though having some sedating and sleep latency-reducing properties, does not primarily act as a sleeping pill, but mainly as a chronobiotic.

To test whether the addition of melatonin to bright-light therapy enhances the efficacy in treating rest-activity (circadian) disruption in institutionalized patients with AD 50 subjects were examined in a randomized, controlled trial [182]. Light treatment alone did not improve nighttime sleep, daytime wake, or rest-activity rhythm while light treatment plus melatonin (5 mg/day) increased daytime wake time and activity levels and strengthened the rest-activity rhythm. In another randomized controlled trial on the effect of bright light and melatonin on cognitive and noncognitive function in 189 elderly residents of group care facilities bright light had a benefit in improving cognitive and noncognitive symptoms of dementia which was amplified by the conjoint administration of melatonin [183]. Melatonin alone had a slight adverse effect on mood. It must be noted that in another double-blind randomized placebo-controlled trial of 24 institutionalized patients with AD another melatonin failed to improve sleep or agitation [184].

Since the circadian oscillator system is obviously affected in AD patients showing severe sleep disturbances, the efficacy of melatonin should be expected to depend heavily on disease progression. One cannot expect a profound inhibition of disease progression once a patient is already in an advanced demented state, notwithstanding a very few case reports with anecdotal evidence of slight mental improvements. Therefore, the use melatonin in the early stages of AD should be important, like MCI.

MELATONIN AND MILD COGNITIVE IMPAIRMENT

MCI is an etiologically heterogeneous syndrome characterized by cognitive impairment shown by objective meas-

ures adjusted for age and education in advance of dementia. Approximately 12% of MCI convert to AD or other dementia disorders every year [12]. Since MCI may represent prodromal AD should be adequately diagnosed and treated [185]. The degenerative process in AD brain starts 20–30 years before the clinical onset of the disease. During this phase, plaques and tangles loads increase and at a certain threshold the first symptom appears. As already mentions, CSF melatonin levels decrease even in preclinical stages when the patients do not manifest any cognitive impairment (at Braak stages I-II) [171], suggesting that the reduction in CSF melatonin may be an early trigger and marker for AD.

With these considerations in mind, we gave melatonin (3 – 9 mg per day) for 9 to 18 months to a group of 25 MCI patients and compare them with a similar group of 25 MCI patients who did not receive melatonin [13]. Patients treated with melatonin showed significantly better performance in Mini–Mental State Examination and the cognitive subscale of the AD Assessment Scale. After application of a neuropsychological battery comprising a Mattis´ test, Digit-symbol test, Trail A and B tasks and the Rey´s verbal test, better performance was found in melatonin-treated patients. Abnormally high Beck Depression Inventory scores decreased in melatonin treated patients, concomitantly with an improvement in wakefulness and sleep quality. The results suggested that melatonin can be a useful add-on drug for treating MCI in a clinic environment [13].

The mechanisms that account for the therapeutic effects of melatonin in MCI patients remain to be defined. In this sense a number of experimental studies indicate that chronic melatonin treatment is very effective to prevent neuronal decay in transgenic models of AD [186,187]. The neuroprotective activity of melatonin against the Alzheimer beta-protein seems not to be mediated by melatonin membrane receptors [188]. Rather most results point out to the strong antioxidative activity of melatonin and its metabolites to achieve these effects [189].

CONCLUSIONS

Normal circadian rhythms are synchronized to a regular 24 h environmental LD cycle. Both SCN and melatonin are essential for this adaptation. Melatonin acts on specific membrane receptors (MT_1, MT_2) to cause these effects.

Desynchronization of circadian rhythms as occurs in chronobiological disorders result in severe disturbances of sleep. Common CRSDs are DSPS, ASPS, non-24-hour sleep/wake rhythm disorder, jet lag, and shift-work. In addition, co-morbidity of severe circadian alterations with neurodegenerative diseases like AD has been documented. Disturbances in the phase position of plasma melatonin levels have been found in all these disorders.

The evidence at present suggests that dysfunctionality in melatonin secretion may play a central role in the pathophysiology of CRSDs. Melatonin has been found useful in treating the disturbed sleep/wake rhythms seen in DSPS, non-24-hour sleep/wake rhythm disorder and irregular type of CRSD, as well as in shift-work sleep disorder and jet lag. A number of melatonin analogs are now in the market that share the potential activity to treat CRSDs [190]. Ramelteon (Rozerem™) is a MT_1/MT_2 melatonin receptor agonist, synthesized by Takeda Chemical Industries with a half-life

much longer (1-2 h) than that of melatonin. Ramelteon acts on both MT_1 and MT_2 melatonergic receptors present in the SCN (for ref. see [191,192]).

Agomelatine (Valdoxan™, Servier) is a novel antidepressant drug which acts as both a melatonin MT_1 and MT_2 receptor agonist and as a 5-HT_{2c} antagonist (for ref see [193,194]). Animal studies indicate that agomelatine accelerates reentrainment of wheel running activity and a study performed in healthy older men indicated that agomelatine phase-shifts 24-h rhythms of hormonal release and body temperature [195].

Vanda Pharmaceutical has completed phase 2 and 3 studies on the melatonin MT_1/MT_2 agonist tasimelteon (VEC-162) and a randomized controlled trial of for transient insomnia after sleep time shift was recently published [196]. After an abrupt advance in sleep time, tasimelteon improved sleep initiation and maintenance concurrently with a shift in endogenous circadian rhythms indicating that it may have therapeutic potential for transient insomnia in CRSDs [196].

Several studies underline the efficacy of melatonin to treat circadian and cognitive symptoms in AD. In this case however the neuroprotective activity of melatonin seems not to be mediated by melatonin membrane receptors but rather by the strong antioxidative activity that melatonin and its endogenous metabolites have. So far none of melatonin analogs has been shown to display such a neuroprotective activity.

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