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Role of the Melatonin System in the Control of Sleep

Therapeutic Implications

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Abstract

The circadian rhythm of pineal melatonin secretion, which is controlled by the suprachiasmatic nucleus (SCN), is reflective of mechanisms that are involved in the control of the sleep/wake cycle. Melatonin can influence sleep-promoting and sleep/wake rhythm-regulating actions through the specific activation of MT_1 (melatonin 1a) and MT_2 (melatonin 1b) receptors, the two major melatonin receptor subtypes found in mammals. Both receptors are highly concentrated in the SCN. In diurnal animals, exogenous melatonin induces sleep over a wide range of doses. In healthy humans, melatonin also induces sleep, although its

maximum hypnotic effectiveness, as shown by studies of the timing of dose administration, is influenced by the circadian phase.

In both young and elderly individuals with primary insomnia, nocturnal plasma melatonin levels tend to be lower than those in healthy controls. There are data indicating that, in affected individuals, melatonin therapy may be beneficial for ameliorating insomnia symptoms. Melatonin has been successfully used to treat insomnia in children with attention-deficit hyperactivity disorder or autism, as well as in other neurodevelopmental disorders in which sleep disturbance is commonly reported.

In circadian rhythm sleep disorders, such as delayed sleep-phase syndrome, melatonin can significantly advance the phase of the sleep/wake rhythm. Similarly, among shift workers or individuals experiencing jet lag, melatonin is beneficial for promoting adjustment to work schedules and improving sleep quality.

The hypnotic and rhythm-regulating properties of melatonin and its agonists (ramelteon, agomelatine) make them an important addition to the armamentarium of drugs for treating primary and secondary insomnia and circadian rhythm sleep disorders.

First identified by Lerner and co-workers in 1958,[1] melatonin (*N*-acetyl-5-methoxytryptamine) is a molecule that is distributed widely in nature, and highly conserved throughout evolution.[2] Melatonin is synthesised primarily in the pineal gland of all animals, and its secretion is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus.[3] Environmental light is the major 'Zeitgeber' synchronising pineal melatonin secretion with the 24-hour day/night cycle. In animals, the pineal gland acts as a 'neuroendocrine transducer' transmitting information regarding day length.[4] By changing the duration of its secretion in cadence with the changes in day length, melatonin is a universal biological signal for darkness and a chemical code for the night.[3] Because of this action, melatonin is able to phase shift the endogenous circadian clock and entrain sleep-wake rhythms.[5] Consistent with these chronobiological effects, MT_1 (melatonin 1a) and MT_2 (melatonin 1b) receptors have been identified in high density in the SCN.[6,7]

It has been suggested that the circadian rhythm of melatonin secretion, with high levels at night and low levels during the day, is reflective of the general mechanism by which sleep is regulated in human beings.[8] The onset of melatonin secretion coincides with the timing of the increase in nocturnal sleepiness.[9-11]

Several lines of evidence have demonstrated the importance of melatonin for the initiation and quality of sleep. For instance, pinealectomy is associated with decrements in the quality of sleep in humans.[12] Furthermore, suppression of melatonin secretion by the use of β-adrenoceptor antagonists has been shown to result in insomnia.[13] With few exceptions,[14,15] impaired melatonin secretion is associated with sleep disorders in elderly individuals with insomnia.[16-21]

By its direct sleep-promoting and circadian phase-shifting effects, melatonin participates in the physiological mechanisms regulating the sleep-wakefulness rhythm.[22] Because of its hypnotic and chronobiotic properties, melatonin is being used successfully for the treatment of age-related insomnia[23] and circadian rhythm sleep disorders such as delayed sleep-phase syndrome, non-24-hour sleep disorder, shift work and jet lag.[24-26]

Melatonin has been identified as an important physiological sleep regulator and as a sleep-wake rhythm-regulating hormone. The aim of this paper is to emphasise the role of melatonin and MT_1/ MT_2 receptors present in the SCN of the hypothalamus (i.e. the melatonin system) in the regulation of sleep. Several studies have demonstrated the importance of melatonin for the initiation, maintenance and quality of sleep (see section 3). In as much as the MT_1/MT_2 receptors mediate the effects of me-

latonin, it is evident that the receptors themselves also form an integral component of sleep regulation. Since melatonin has a short half-life, the newly developed melatonin agonists, which have a comparatively greater affinity for melatonin receptors, and, furthermore, which interact with MT_1/MT_2 receptors both in the SCN and in other brain areas, are of particular interest from a clinical point of view. These agents have been found to be quite effective in reducing sleep latency, improving sleep efficiency, increasing total sleep time and regulating sleep-wake rhythm (see section 5.1.2). Ramelteon is a specific MT_1/MT_2 receptor agonist that has a duration of action that is greater than that of melatonin itself. This recently introduced hypnotic agent has demonstrated efficacy as a combined 'chrono-hypnotic' drug. The overall efficacy of ramelteon, which is superior to that of melatonin itself, supports the inference that it is the 'melatonin system' rather than melatonin that contributes to the effective regulation of sleep. Agomelatine is another MT_1/MT_2 receptor agonist with high affinity for melatonin receptors. This dual-action drug has been found to be effective in treating sleep problems in patients with major depressive disorder and other mood disorders.

PubMed was searched using Entrez for articles published up to 15 January 2007, including electronic early-release publications. Search terms included 'melatonin', 'sleep disorders', 'ramelteon' and 'agomelatine'. Full publications were obtained and references were checked for additional material where appropriate.

1. Melatonin Biosynthesis and Metabolism

Melatonin biosynthesis occurs primarily in the pinealocytes of all animals. Synthesis also occurs in other areas such as the retina,[27,28] gastrointestinal tract,[29,30] skin,[31] lymphocytes,[32] platelets[33] and bone marrow cells.[34]

Tryptophan acts as the precursor for the biosynthesis of melatonin. It is taken up from the blood and is converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase. The next step in melatonin biosynthesis is the conversion of 5-hydroxytryptophan into serotonin (5-hydroxytryptamine; 5-HT) by the enzyme aromatic amino acid decarboxylase. Serotonin is acetylated to form *N*-acetylserotonin by the enzyme arylakylamine-N-acetyltransferase (AA-NAT). *N*-Acetylserotonin is then converted into melatonin by the enzyme hydroxyindole-*O*-methyltransferase. Once formed in the pineal gland, melatonin is released into the capillaries and in higher concentrations into the CSF,[35] and is then rapidly distributed to most body tissues.[36] Melatonin attains maximal plasma levels between 2:00 and 3:00am.

Although melatonin biosynthesis occurs in many tissues, circulating melatonin is almost totally derived from the pineal gland. Since there is no storage of melatonin in the pineal gland and, furthermore, since circulating melatonin is rapidly metabolised in the liver, the levels of melatonin or its metabolite 6-sulfatoxymelatonin (aMT6s) in plasma or saliva are truly reflective of pineal melatonin biosynthetic activity.[37]

The half-life of melatonin exhibits a biphasic pattern, with a first distribution half-life of 2 minutes and a second distribution of 20 minutes.[3] A clearance rate from the peripheral circulation with half-lives of 3 and 45 minutes has been reported.[38]

For many years, melatonin was thought to be almost exclusively catabolised by hepatic cytochrome P450 (CYP) mono-oxygenases, followed by conjugation of the resulting 6-hydroxymelatonin, to give the main urinary metabolite aMT6s. This may be largely true for the circulating hormone, but not necessarily for tissue melatonin. Particularly in the CNS, oxidative pyrrole ring cleavage prevails and no 6-hydroxymelatonin has been detected after melatonin injection into the cisterna magna.[39] This may be particularly important because much more melatonin is released via the pineal recess into the CSF than into the circulation.[35] The primary cleavage product is N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), which is deformylated, either by arylamine formamidase or hemoperoxidases to N^1-acetyl-5-methoxykynuramine (AMK).[40] Surprisingly, numerous (enzymatic [indoleamine 2,3-dioxygenase, myeloperoxidase], pseudoenzymatic [oxoferryl haemoglobin, hemin], photocatalytic or free radical) reactions lead to formation of the same product, AFMK. Some estimations have revealed that pyrrole ring cleavage contributes to about one-third of the total catabol-

ism, but the percentage may be even higher in certain tissues.[40] Other oxidative catabolites are cyclic 3-hydroxymelatonin, which can also be metabolised to AFMK, and a 2-hydroxylated analogue, which does not cyclize, but turns into an indolinone.

While the pharmacokinetics of exogenous melatonin, including its half-life and clearance, are relatively uniform in laboratory rodents, in humans it has a limited bioavailability, as well as a highly variable pharmacokinetic profile. The low bioavailability of orally administered melatonin has been attributed to a first-pass effect through the liver and to the activity of gastrointestinal CYP, which metabolises a substantial amount of the neurohormone.

The bioavailability of melatonin in females is 2-fold greater than that in males.[41] Substantial individual variations in melatonin bioavailability have been reported, with interindividual differences as high as 37-fold.[40] The large individual variation in the bioavailability of melatonin is attributed to the high variability of CYP subtype gene expression in humans. This may perhaps account for differential responses seen in individuals who take melatonin orally.

The bioavailability of melatonin is increased by the concomitant intake of either fluvoxamine (an SSRI),[42] caffeine,[43] or vitamin E or C.[40] Indeed, there is much to be understood regarding the pharmacokinetics of exogenous melatonin before a clear picture of its action in human beings can be obtained.

1.1 Regulation of Melatonin Biosynthesis

The circadian activity of the SCN is synchronised to the light/dark cycle mainly by light perceived by the retina. The signal generated in the retina is transmitted to the SCN through a monosynaptic retino-hypothalamic tract that has its origin in the ganglion cell layer of the retina.[44] These specialised ganglion cells use glutamate as a neurotransmitter and, presumably, pituitary adenylate cyclase activating polypeptide.[45] Differing from other retinal ganglion cells, the cells that innervate the SCN contain the photopigment melanopsin and, thus, are directly sensitive to light.[46,47]

A major projection of the SCN is to the subparaventricular zone of the hypothalamus and, from there, to areas involved in sleep/wake regulation.[48] Other SCN projections go via the paraventricular nucleus to the median forebrain bundle and reticular formation, and then make synaptic connections with the cells of the intermediolateral columns of the cervical spinal cord, from which preganglionic sympathetic fibres of the superior cervical ganglia (SCG) arise.[49] The postganglionic sympathetic fibres from the SCG reach the pineal gland and stimulate it by releasing noradrenaline (norepinephrine) from their nerve endings. Activation of the β-adrenoceptors present on the pinealocytes results in increased cyclic adenosine monophosphate (cAMP) concentration that promotes the biosynthesis of melatonin.[50] α_1-Adrenoceptors potentiate β-adrenergic activity by producing a sharp increase in intracellular Ca^{2+} and activation of protein kinase C and prostaglandins.[51-53] Activation of an inducible cAMP repressor gene is presumably a central phenomenon in the control of nocturnal melatonin production.[54]

During the day, noradrenaline release from the postganglionic sympathetic nerve fibres is suppressed because of an increased electrical activity in the SCN. At night, when SCN activity is inhibited, the release of noradrenaline is enhanced.[55] The action spectrum for the suppressive effect of light on pineal melatonin secretion indicates a peak at the short wavelengths of light (446–477nm),[47] coinciding with the spectrum absorption of the melanopsin photopigment.

Pineal melatonin production exhibits a circadian rhythm, with low levels during the day and high levels at night. This circadian rhythm persists in all living organisms, ranging from algae to humans, irrespective of whether the organisms are active during the day or night.[3] Although AA-NAT has long been considered as the rate-limiting step in melatonin synthesis, recent studies indicate that hydroxyindole-*O*-methyltransferase (HIOMT) may play such a role. Initial studies on the Siberian hamster pineal gland[56] were confirmed by other studies documenting that an elevated AA-NAT activity induced by exposure to both α- and β-adrenoceptor agonists failed to promote melatonin production; indeed, the increased activity of HIOMT did correlate with an increase in melatonin production.[57] In a genetic mutant model with a mutation of

the *AA-NAT* gene, i.e. a Long Evans cinnamon rat,[58] the *H28Y* mutation resulted in low expression and poor stability of AA-NAT protein, with pineal AA-NAT activity being reduced by 90% compared with the wild-type counterpart. However, in those rats, melatonin synthesis did not decline and the levels of *N*-acetylserotonin exhibited no relation with pineal melatonin concentration. Therefore, downstream mechanisms after AA-NAT seem to be involved in the regulation of melatonin synthesis.[58]

2. Melatonin Receptors

Melatonin partly exerts its physiological actions by acting on MT_1 and MT_2 receptors.[59,60] Both receptors belong to the superfamily of G-protein-coupled receptors containing the typical seven transmembrane domains.[61] These two receptor subtypes are responsible for the sleep promoting and circadian effects of melatonin. MT_2 receptors are responsible for inducing phase shifts; hence, they are involved in the entrainment of circadian rhythmicity.[7] MT_1 receptors are responsible for suppression of firing in the neurons of the SCN;[6] thus, they are concerned with the regulation of the amplitude of circadian rhythmicity.

In humans, the expression of MT_1 and MT_2 receptor subtypes in the SCN has been documented.[62] As demonstrated in rodents, the administration of melatonin at times that correspond to dusk or dawn causes phase shifts in the circadian rhythm of electrical activity recorded from SCN neurons. Administration of melatonin at other times had little or no effect on SCN clock mechanisms.[63] A third binding site, initially described as an MT_3 receptor, has been subsequently characterised in hamsters as the enzyme quinone reductase-2[64] and plays no role in the entrainment or amplitude of SCN neuronal function.

The expression of MT_1 receptors in the human SCN decreases with advancing age as well as in the late stages of Alzheimer's disease.[65] Sleep disruptions, nightly restlessness and circadian rhythm disturbances seen in the elderly and in patients with Alzheimer's disease may be due to alterations of MT_1 receptor expression found in the SCN.

3. Melatonin and Sleep

Melatonin has been identified as an important physiological sleep regulator. The increase in sleep propensity (tiredness) at night usually occurs 2 hours after the onset of endogenous melatonin production.[9,11] Sleep is a state characterised by alternating patterns of neural activity, which is controlled by homeostatic and circadian mechanisms. As sleep regulatory mechanisms, these two processes are closely interactive and interdependent.[66,67] The homeostatic need for sleep depends upon mutually inhibitory interactions between sleep and arousal promoting systems. Slow-wave sleep is primarily controlled by the homeostatic process (i.e. the length of prior wakefulness), whereas the timing of sleep onset and offset, as well as the distribution of rapid eye movement (REM) sleep, are controlled by the circadian system.[66,67]

In general, sleep and waking performance represent complex behaviours generated by a variety of neuroanatomical structures such as the brainstem, hypothalamus, thalamus and neocortex.[68] The daily rhythms in sleep and waking performance are generated by the interplay of multiple external oscillators such as light/dark cycles, and internal oscillators such as the SCN and homeostatic oscillators, which are driven mainly by sleep-wake behaviour.[69] It is generally accepted that the circadian system originating in the SCN promotes wakefulness. The SCN also has an active role in promoting sleep during the quiescent phase of the circadian rhythm.[70]

The mechanism by which the SCN promotes sleep is still under investigation; however, a number of studies suggest that melatonin is the principal neurochemical agent through which it achieves this.[71] The finding that melatonin is secreted primarily during the night,[72] and the close relationship between the nocturnal increase of endogenous melatonin and the timing of human sleep[73] have pointed to the importance of melatonin in sleep regulation. The activity of exogenous melatonin in promoting sleep has been documented by neuroimaging procedures in healthy volunteers.[74]

The onset of night-time melatonin secretion occurs approximately 2 hours before an individual's habitual bedtime and has been shown to correlate

well with the onset of evening sleepiness.[13,75,76] Suppression of melatonin production by procedures such as treatment with β-adrenoceptor antagonists has been shown to correlate with insomnia.[77,78] Conversely, increasing plasma melatonin concentrations by the suppression of melatonin-metabolising enzymes in the liver resulted in increased sleepiness.[79]

In a study conducted by Haimov and Lavie,[80] a temporal relationship between the nocturnal increase of endogenous melatonin and the 'opening of the sleep gate' was found. Upon administration of melatonin in the afternoon, the sleep gate was advanced by 1–2 hours, while exposure to 2 hours of bright evening light between 8:00 and 10:00pm delayed the next-day rise in nocturnal increase of melatonin and the opening of the sleep gate.[80] The period of wakefulness immediately prior to the opening of the sleep gate is referred to as the wake-maintenance zone or 'forbidden zone' for sleep.[81,82] During this time the sleep propensity is lowest because of the increased activity of SCN neurons.[83,84]

The transition phase from wakefulness/arousal to high sleep propensity coincides with the nocturnal rise in endogenous melatonin.[8] It was therefore proposed that melatonin contributes to the opening of the gate of nocturnal sleepiness by inhibiting the circadian wakefulness-generating mechanism.[9,85,86] This effect is thought to be mediated by MT_1 receptors at the SCN level.[6,87] Melatonin is released in pulses during stages of light sleep and its function is to induce deep sleep and to prevent awakening by inhibiting the firing of SCN neurons.

3.1 Effects in Animal Models

Melatonin is temporally and functionally associated with sleep only in diurnally active species. For this reason, most rodents are not suitable as test organisms for sleep experiments with melatonin. In a study by Zhdanova and co-workers,[88] diurnal macaques were chosen as an animal model for exploring the nature of sleep-promoting effects of melatonin. Because of their close phylogenetic similarity to human beings, diurnally-active macaques share a number of behavioural and physiological commonalities with humans, including their pattern of sleep and sleep regulatory mechanisms. The SCN activity pattern in diurnal macaques is identical to that found in humans, with high activity of SCN neurons occurring during the day, correlating with daytime activity. This is followed by a decrease in SCN activity pattern at night. Moreover, these animals also exhibit a similar temporal pattern of melatonin production occurring during their habitual night-time period.[88] In macaques, as in humans, administration of melatonin over a wide range of doses (5–20 μg/kg orally) promoted sleep initiation.[88] In macaques, sleep processes are also closely influenced by the time at which melatonin is administered, with daytime administrations showing measurable effects on sleep induction.[89] These findings in macaques suggest that overall melatonin levels, even those present during the day, are perhaps a key factor affecting sleep quality.[88] This variable needs to be studied more closely in human sleep disorders, particularly in insomnia.

In non-mammalian diurnal vertebrate species (e.g. pigeons), daytime melatonin administration induced daytime sleep as well as increased EEG slow-wave activity, but did not alter subsequent sleep at night.[90] In house sparrows and Japanese quail, melatonin reduced locomotor activity.[91] In the zebrafish, which is used as a favorite model for studying vertebrate genetics, melatonin has a sleep-promoting effect.[92] Collectively, the studies on various animal models indicate that the acute sleep-promoting effect of melatonin is not unique to human beings, but is also seen in other diurnal species.[93] However, it should be kept in mind that birds and fish differ from mammals in brain sensitivity to light and the effect of melatonin on these structures may be different to that of mammals.

3.2 Effects on Sleep in Humans

Initially, the inference that melatonin might be involved in the physiological regulation of sleep in humans was based on correlational findings that it was secreted primarily at night and that it had a close temporal relationship to the timing of human sleep onset and maintenance. The first strong evidence of the sleep-promoting effects of melatonin was provided by Lerner and Case.[94] In an attempt to treat patients with vitiligo, the investigators found that melatonin administration caused the patients to become sleepy.[94] The early observations of Lerner

and Case[94] were based mainly on subjects' self reports. The original study was followed up by studies including polysomnographic (PSG) assessments in which administration of melatonin across a wide range of doses was found to induce sleep without causing any adverse effects. Even very high doses did not cause uncontrollable sedation or anaesthesia.[95,96] The sleep-inducing effects of melatonin at pharmacological doses >1mg were confirmed by many other investigators.[97-100] Some of these initial studies used very high doses ranging from 50–1000mg orally or 200mg intravenously.

In response to skepticism that the high pharmacological melatonin doses truly promoted sleep, further studies were conducted using doses close to the physiological range. In 1994, Dollins and co-workers[101] published their results on the effects of daytime doses of melatonin ranging from 0.1–10mg on sleep in young healthy individuals. In this study, 'physiological doses', i.e. those that were sufficient to elevate blood or serum concentrations to nocturnal melatonin levels considered normal, were used. Administration of melatonin 0.1–0.3mg, resulting in circulating melatonin levels <200 pg/mL (close to the maximum levels found at night), had a sleep-promoting effect in young healthy volunteers.[101]

PSG studies using physiological doses of melatonin, administered either at different times of the day or 2 hours prior to the subject's habitual bedtime, were found to significantly promote sleep onset.[76,102] These studies showed that physiological circulating melatonin levels can, if initiated prior to habitual hours of sleep, accelerate sleep onset.[93] Moreover, the efficacy of the dose of melatonin, i.e. whether it was provided in physiological or pharmacological doses, appeared to make little difference in terms of its effect on sleep onset. This was demonstrated in a study in which a comparison of different doses (0.1, 0.5, 1, 5 or 10mg) administered either during the evening prior to a nap or before nighttime sleep, demonstrated clear effects on sleep onset in young healthy volunteers but did not produce any further improvements in sleep quality.[103] In another study, 5mg of melatonin administered at four different times during the day promoted sleep following each administration, as demonstrated by EEG-measured increases in θ- and δ-waves, and spindle bursts, as well as by increases in subjective reports of sleepiness.[104] The latency to maximum hypnotic activity after melatonin administration varied linearly from 3 hours 40 minutes at noon, to 1 hour after melatonin administration at 9:00pm.[104] Morning administration of melatonin delays the onset of evening sleepiness, while evening administration advances sleep onset.[105] The phase-shifting effects of a slow-release preparation of melatonin (1.5mg) on sleep was evaluated using PSG,[106] and plasma melatonin levels of 625 pg/mL, about 10-fold greater than normal nocturnal peak melatonin values, were found to be effective. In this study melatonin exerted both direct (hypnotic) and circadian effects on sleep.[106]

The regular nocturnal increase in endogenous melatonin release has been identified in a large number of studies as an important determinant of sleep timing in sighted as well as blind individuals.[107-110] Lockley et al.[108] and Sack et al.[109] chose fully blind individuals, i.e. those with a complete lack of light perception and who had an inability to entrain their circadian rhythms to an external 24-hour day/night cycle (non-24-hour sleep/wake disorder), for a study of the entrainment effects of melatonin administration. Melatonin doses ranging from 0.5mg to 10mg improved the individuals' nocturnal sleep, and additionally entrained their circadian rhythmicity to a 24-hour day/night cycle.[108,109] The effects of melatonin on sleep initiation normally occur within 30–60 minutes after administration, a delay that may correspond to the activation time of SCN melatonin receptors.

A recent double-blind, placebo-controlled study was carried out to investigate the effects of physiological (0.3 mg/day) and pharmacological (5 mg/day) dosages of exogenous melatonin on sleep latency and sleep efficiency in healthy individuals. Using a 27-day forced desynchrony paradigm and a 20-hour scheduled sleep-wake cycle, the investigators studied the effects of the two dosages across a full range of circadian phases.[111] Both dosages of melatonin improved PSG-determined sleep efficiency from 77% (placebo) to 83%. Melatonin did not significantly affect sleep initiation or core body temperature (cBT). The authors concluded that exogenous melatonin administration can be as affective as endogenous melatonin release for regulating the circadian phase. These findings thus demonstrated that

exogenous melatonin administration could have potential therapeutic value for bringing disordered sleep patterns under control.[111]

An increasing amount of evidence has shown that a reduction in endogenous melatonin production seems to be a prerequisite for the effective treatment of sleep disorders with exogenous melatonin. A recent meta-analysis of the effects of melatonin in sleep disturbances, including all age groups (and presumably individuals with normal melatonin levels), failed to document significant and clinically meaningful effects of exogenous melatonin on sleep quality, efficiency or latency.[112] It must be noted that a statistically nonsignificant finding indicates that the alternative hypothesis (e.g. melatonin is effective in decreasing sleep-onset latency) is not likely to be true, rather than that the null hypothesis is true (which in this case is that melatonin has no effect on sleep-onset latency), because of the possibility of a type II error. By combining several studies, meta-analyses provide better size effect estimates and reduce the probability of a type II error, making false-negative results less likely. Nonetheless, this does not seem to be the case in the study of Buscemi et al.,[112] which consisted of a sample of <300 individuals. Reviewed papers showed significant variations in the route of administration of melatonin, the dosage administered and the way in which outcomes were measured. All of these drawbacks resulted in a significant heterogeneity index and in a low quality size effect estimation (shown by the wide 95% confidence intervals reported).[112]

In contrast, another meta-analysis derived from 17 different studies, involving 284 subjects, most of whom were older, revealed that exogenous melatonin significantly reduced sleep-onset latency, increased sleep efficiency and increased total sleep time.[110] Based on this meta-analysis, the use of melatonin in the treatment of insomnia, particularly in aged individuals with nocturnal melatonin deficiency, was proposed. However, it is important to note that an effect on total sleep time in the presence of effects on sleep-onset latency cannot be totally construed as evidence for an effect on sleep maintenance, without the demonstration of a significant decrease in wakefulness after sleep onset. Melatonin treatment decreased wakefulness after sleep onset in some specific studies[78,113] but not in another.[114] In the study by Hughes and co-workers,[114] PSG measures confirmed that sleep latency was reduced following both physiological and pharmacological dosages of melatonin with absence of effects on wakefulness after sleep onset or sleep efficiency, demonstrating that high physiological dosages of melatonin can promote sleep.

4. Mechanism of Hypnotic Action

It has been suggested that the hypnotic action of melatonin is due to its effect on the MT_1 receptor subtype,[93] and that it is through this receptor that the wakefulness-inducing activity of the SCN is suppressed.[6,7] SCN neurons are active during the day and are relatively quiet at night, having a similar temporal pattern of activity and quiescence in nocturnal animals; therefore, the SCN activity *per se* may have no direct alerting effect. Promotion of sleep by melatonin has been shown to correlate with reductions in brain cAMP levels.[93]

A poorly known aspect of melatonin activity in the brain is the extent to which it desensitises receptors. Receptor desensitisation is a normal process in the regulation of signal transduction. As desensitisation is a common phenomenon in G-protein-coupled receptors, this also has to be expected for MT_1 and MT_2 receptors. In fact, desensitisation has been observed with both receptor subtypes and, in particular, in association with C-terminal phosphorylation and arrestin-dependent internalisation.[115,116] However, most studies of this effect have been conducted in highly artificial systems, e.g. in Chinese hamster ovary cells transfected with the human receptor genes. The critical research question therefore is whether the dynamics of desensitisation are the same as those seen *in vitro* and, more particularly, in the SCN as a specific, sleep-relevant target.

An earlier investigation indicated that no desensitisation occurs in the SCN, neither *in vivo* (intraperitoneal or iontophoretic application of melatonin) nor in SCN slices *in vitro*.[117] However, a more recent study conducted on immortalised SCN cells indicated strong desensitisations of the MT_2 receptor by melatonin exposure.[118,119] The effects observed were remarkably long lasting and might explain some aspects of the phase-response curve for melatonin in the SCN, particularly the

duration of the dead zone, in which any phase shifting is impossible or negligible.

Since physiological amounts of melatonin may be able to desensitise the endogenous melatonin receptors in the rat SCN,[118,119] the supraphysiological doses of melatonin usually employed to treat individuals with insomnia might be expected to work for just a few days, but not necessarily over the long term. It must also be noted that the level of expression of melatonin receptors in the SCN is very low during the day and high at night, when melatonin levels are also high.[120] The parallel increase in melatonin receptor density and melatonin concentration raises doubt about the theory of a receptor desensitisation phenomenon after long-term use of melatonin (or its agonists).

A probable mechanism to explain the paradoxical link between CNS melatonin levels and receptor density has recently been identified by demonstrating that long-term melatonin exposure produces microtubule rearrangements that enhances protein kinase C activation (which modulates melatonin receptor function through its action on G-proteins).[121] Thus, receptor sensitivity can be sustained for a long time after melatonin exposure.

Melatonin, when administered in doses ranging from 0.1 to 10mg in the evening, or prior to a nap, or before night-time sleep, promotes sleep onset.[93] Although physiological and pharmacological doses of melatonin are significantly different in terms of efficacy, there are individual variations in melatonin receptor sensitivity, as revealed by the observation that some young healthy individuals did not demonstrate any sleep-promoting effect of melatonin, independently of the dose used.[93]

Hence, individual variations in melatonin receptor sensitivity (in addition to differences in the bioavailability of melatonin, as discussed above)[40] could account for the range of responses to the sleep-promoting effect of melatonin seen in humans. Furthermore, long-term clinical studies on the use of melatonin in the treatment of sleep disorders are required before the issue of desensitisation of melatonin receptors can be fully defined.

Ramelteon, like melatonin, acts on MT_1 and MT_2 receptors, but with a higher affinity, i.e. nearly 3- to 16-fold greater than that of melatonin.[122] Unlike melatonin, it has negligible affinity for the quinone reductase-2 enzyme (the so-called 'MT_3' receptor). It has been suggested that significant receptor densensitisation is likely to occur with long-term use of ramelteon.[123] This needs careful evaluation in large-scale studies of ramelteon in patients with insomnia.

Since the absolute bioavailability of ramelteon following an oral dose of 16mg is low because of its extensive first-pass hepatic metabolism,[124] doses of ramelteon are usually higher than those of melatonin. As has already been pointed out with melatonin, a parallel increase in melatonin receptor density following long-term exposure to ramelteon might help to prevent the desensitisation phenomenon.

The novel mechanism of action of ramelteon has prompted larger questions regarding the sleep-promoting effects of melatonin itself. In as much as sleep is normally accompanied by a decline in cBT,[113,125] some have suggested that it is the effect of melatonin on the thermoregulatory centres that underlie its hypnotic effects.[126] Initially, this hypothesis was rejected in view of evidence showing that the temporal patterns of sleep were not synchronous with those of temperature. In more recent studies, however, it has been shown that, when compared with placebo, melatonin administration not only increases sleepiness but also produces a concomitant reduction in cBT. By using the cold thermic challenge test, it was shown that the sleep-inducing effects of melatonin occurred in parallel with a reduction in the thermoregulatory set point. By regulating the fine-tuning of the peripheral vascular bed, melatonin may participate in thermoregulatory mechanisms intimately coupled to its ability to increase sleepiness and to induce sleep;[127] however, this conclusion is open to debate, since low doses of melatonin induced sleep, with quite small or no modifications in cBT.[23,111]

5. Efficacy of Melatonin in Clinical Situations

5.1 Insomnia

Approximately 30–35% of the adult population experience occasional or intermittent sleep disturbances.[128] The risk of insomnia is greatest in the

elderly, i.e. those aged ≥65 years. Insomnia is a sleep disorder characterised by poor quality of sleep resulting from one or more of the following symptoms: difficulty in falling asleep, awakening frequently during the night and/or early morning awakenings.

Insomnia is often a symptom of psychological or physiological problems. Mental disorders are the leading cause of secondary insomnia.[129] In as much as insomnia causes decreased memory, concentration, fatigue, anxiety and impaired performance, it has a major negative impact on the health-related quality of life of affected individuals.[130]

Owing to its broad-ranging effects on other health parameters, insomnia is now seen as an important contributor to the more commonly cited causes of human mortality,[131] thus supporting the conclusion that efforts to improve sleep in individuals with insomnia would represent a significant contribution to the promotion of human longevity.[132] A growing realisation of the close linkage between quality of sleep and human health has, in recent years, prompted intense scientific interest in this association, particularly as it applies to insomnia in the elderly.

While most studies have documented a significant correlation between low melatonin production and insomnia,[16-21] others have reported either a tendency or no correlation between these variables.[14,15,114] In a study of elderly women with complaints of poor sleep, urinary aMT6s excretion was significantly lower than that in individuals who were able to sleep well.[17] In young and middle-aged individuals with primary insomnia, lower nocturnal plasma melatonin concentrations were evident compared with healthy controls.[18] A clinical study undertaken in 517 individuals aged >55 years revealed that those experiencing insomnia had significantly lower levels of nocturnal aMT6s excretion.[19] Individuals (aged 25–65 years) with primary insomnia were found to have abnormal melatonin rhythms when compared with age-matched controls.[20] Not only was the total amount of melatonin secreted in elderly individuals with insomnia reduced, but the peak in its output was delayed when compared with healthy controls.[16] Disturbed excretion rhythms of aMT6s have also been reported in elderly individuals with insomnia or depression;[21] however, low aMT6s levels were found in elderly individuals with insomnia as well as in controls who were able to sleep well.[15] As noted by Zhdanova,[93] all studies relating to circulating melatonin levels and incidence of insomnia were cross-sectional, rather than longitudinal, a very important point in as much as there is high interindividual variability in circulating melatonin levels at every age group.

If melatonin deficiency is a cause rather than a marker for insomnia, melatonin replacement therapy should be beneficial in the treatment of insomnia. Indeed, several studies have demonstrated the beneficial effects of melatonin and its analogues (ramelteon, agomelatine) in insomnia and for secondary sleep disorders.[19,110,111,133-139]

5.1.1 Melatonin in the Treatment of Insomnia

It has been suggested that melatonin, because of its low toxicity and lack of adverse effects, may be an ideal hypnotic agent for use in aged individuals with insomnia.[93] In a study of elderly patients with insomnia, administration of melatonin 1 and 5mg was found to improve subjective reports of sleep quality.[140] In other studies, administration of a controlled-release melatonin formulation (2 mg/day) for 1 week in melatonin-deficient individuals with insomnia increased sleep efficiency and reduced nocturnal awakenings after sleep onset.[141] This was confirmed by other studies in which administration of 2 mg/day of the controlled-release formulation for 3 weeks to elderly individuals with insomnia also resulted in improvement of sleep efficiency and reduced the number of awakenings after sleep onset (table I).[133]

Physiological doses of melatonin (0.3–0.5mg) also improved sleep quality in elderly individuals with insomnia. In a study by Hughes et al.[114] PSG confirmed that sleep latency was reduced following both physiological and pharmacological doses of melatonin without effects on wakefulness after sleep onset. In contrast, Zhdanova and co-workers[23] found that while both physiological (0.1 and 0.3mg) and pharmacological (3.0mg) doses of melatonin improved sleep efficiency, they did not produce significant changes in sleep-onset latency. The latter study is important because it proved that doses of melatonin that raise the plasma melatonin levels within its normal nocturnal surge (60–200 pg/mL)

Table I. Double-blind, placebo-controlled studies on the use of melatonin for the treatment of primary and secondary insomnia

Medical condition	Dosage of melatonin (mg/day)	Duration of treatment	No. of patients	SOL	SQ	TST	SE	Type of study	Reference
Primary insomnia	1 and 5	1wk	10	↓	↑	↓	NA	Subjective and PSG	140
Age-related insomnia	2	3wk	12	↓	NA	NC	↑	Actigraphy	133
Age-related insomnia	2	1wk	51	↓	NA	NC	↑	Actigraphy	134
Primary insomnia	5	>1wk	15	NC	↑	NC	NA	Subjective	142
Age-related insomnia	0.5	2wk	14	↓	NC	NC	NC	Subjective, PSG and actigraphy	114
Secondary insomnia (schizophrenia)	2	3wk	19	↓	NA	↑	↑	Actigraphy	143
Age-related insomnia	0.1, 0.3 and 3	1wk	15	NC	NA	NC	↑	Subjective, PSG and actigraphy	23
Secondary insomnia (stroke, cardiovascular disease, diabetes mellitus)	5.4	1–2wk	33	↓	↑	↑	NA	Subjective	144
Sleep-onset insomnia	5	4wk	40	↓	NA	↑	NA	Subjective and actigraphy	145
Sleep-onset insomnia	5	4wk	62	↓	NA	↑	NA	Subjective	146
Secondary insomnia (Alzheimer's disease)	2.5	8wk	157	NA	↑	↑	NA	Subjective and actigraphy	147
Secondary insomnia (Alzheimer's disease)	3	4wk	11	NA	NA	↑	NA	Actigraphy	148
Sleep-onset insomnia	2	2.1 ± 2.0mo	29	↓	NA	NA	NA	Subjective	149
Secondary insomnia (asthma)	3	4wk	22	NA	↑	NA	NA	Subjective	150
Age-related insomnia	2	3wk	112	NA	↑	NA	NA	Subjective	19
Secondary insomnia (Parkinson's disease)	5 or 50	2wk	40	↓	↑	↑	↑	Subjective and actigraphy	151
Secondary insomnia (attention-deficit hyperactivity disorder)	5	30 days	27	↓	↑	↑	NA	Subjective	152

NA = not assessed; **NC** = no change; **PSG** = polysomnographic; **SE** = sleep efficiency; **SOL** = sleep-onset latency; **SQ** = sleep quality; **TST** = total sleep time; ↑ indicates increase; ↓ indicates decrease.

can significantly improve sleep in people experiencing age-related insomnia.

In a study involving a large number of patients (330 men and 187 women) aged ≥55 years, 396 patients were treated with placebo and melatonin (mean baseline excretion of aMT6s, 8.9 ± 7.8 μg/night).[19] Of these 396 patients, 372 provided complete datasets and were divided into six groups, based on their baseline aMT6s excretion. As indicated by the proportions of 'responders' to melatonin replacement therapy, those who had the lowest levels of nocturnal aMT6s excretion (<3.5 μg/night; n = 112) showed the greatest therapeutic gains. Based on these observations, the investigators concluded that melatonin replacement therapy is beneficial in patients with low melatonin production.[19] It was further observed that the decline in melatonin production with age or disease impairs sleep in older patients. There is evidence that age is also a moderating variable for melatonin therapy itself. In a study of the effect of exogenous melatonin administration among the elderly, subjective improvement in sleep quality was reported.[142]

Secondary insomnia is a common medical situation. In a study conducted on 33 medically-ill patients (cerebrovascular disease, cardiovascular disease and diabetes mellitus) administration of melatonin (average daily dose of 5.4mg) for a period ranging from 8 to 16 days significantly improved sleep quality, shortened sleep onset and increased total sleep time.[144] Oral melatonin 3 mg/day significantly improved subjective sleep quality compared with placebo (p = 0.04) in a 4-week randomised, double-blind trial in 22 patients with asthma.[150] A double-blind, placebo-controlled crossover trial performed in 40 patients with Parkinson's disease treated for 2 weeks with melatonin 5 or 50 mg/day indicated a significant improvement in total nighttime sleep time, sleep quality and daytime sleepiness.[151]

Insomnia is a common symptom among psychiatric patients. In a randomised, double-blind crossover trial of 19 schizophrenic patients, administration of sustained-release melatonin 2 mg/day for 3 weeks significantly improved sleep efficiency and increased total sleep time compared with placebo.[143]

5.1.2 Melatonin Agonists in the Treatment of Insomnia

In view of the short half-life of melatonin, it has been proposed that melatonin analogues with longer lasting effects could have even greater potential value for treating sleep disorders.[153] Ramelteon is a tricyclic synthetic analogue of melatonin that has been approved by the US FDA for the treatment of insomnia. This drug has a longer half-life than melatonin and a high affinity for MT_1 and MT_2 receptors. An additional advantage of ramelteon, as well as that of a similar agent, agomelatine, over conventional hypnotic drug therapies is their adverse effect profiles, having virtually none of the adverse effects reported with benzodiazepines.[154]

In clinical trials, ramelteon has shown promising results in the treatment of transient and chronic insomnia (table II).[155] In a PSG study of patients with chronic insomnia, ramelteon 4, 8, 16 or 32 mg/day significantly reduced sleep-onset latency and increased total sleep time, with little or no effect on wakefulness after sleep onset.[137] Furthermore, the drug produced no next-day residual or adverse effects.[136,137] The effects of ramelteon were investigated in 829 patients, aged ≥65 years, with chronic insomnia.[156] The patients were randomised to receive placebo, ramelteon 4 or 8 mg/day, and were treated for a period of 5 weeks. Ramelteon 4 mg/day resulted in significant increases in total sleep time after 1 or 3 weeks. Significant reductions in sleep-onset latency were noted after 5 weeks of treatment with ramelteon. Ramelteon, with its novel mechanism of action, is considered to be a promising drug for effective treatment of insomnia.[157]

Ramelteon exerts its hypnotic activity both directly and through its metabolite M-II. M-II also binds with MT_1 and MT_2 receptors, but with an affinity that is one-tenth and one-fifth, respectively, of the parent compound.[156] The half-life of ramelteon is short and the drug does not seem to accumulate in the brain after repeated administration.[158] The absolute bioavailability of ramelteon following an oral dose of 16mg is low (<2%; range 0.5–12%);[124] because of the extensive first-pass hepatic metabolism, the administered dose of ramelteon is usually higher than that of melatonin. It has been suggested that a significant receptor densensitisation is likely to occur with long-term use of ramelteon, in view of

Table II. Double-blind, placebo-controlled studies on the use of ramelteon or agomelatine for the treatment of insomnia

Medical condition	Dosage (mg/day)	Duration of treatment	No. of patients	SOL	SQ	TST	SE	Type of study	Reference
Ramelteon									
Transient insomnia induced by sleeping in a novel environment	16 or 64	1 night	375	↓	NA	↑	NC	PSG	136
Primary insomnia	4, 8, 16 or 32	2 nights	107	↓	NA	↑	↑	PSG	137
Primary insomnia	4 or 8	5wk	829	↓	↑	↑	NA	Subjective	156
Agomelatine									
Major depressive disorder	25	5wk	332	↓	↑	NA	NA	Subjective, PSG	139

NA = not assessed; **NC** = no change; **PSG** = polysomnographic; **SE** = sleep efficiency; **SOL** = sleep-onset latency; **SQ** = sleep quality; **TST** = total sleep time; ↑ indicates increase; ↓ indicates decrease.

the doses employed (see section 4).[123] This issue needs to be evaluated in large prospective studies on ramelteon in patients with insomnia.

As reported in the prescription information available from the manufacturer,[159] in a study of 122 individuals with chronic insomnia of 6 months' duration, ramelteon 16 mg/day was found to be associated with increased serum prolactin level. Overall, the mean serum prolactin level change from baseline was 4.9 μg/L (a 34% increase) for women in the ramelteon group compared with −0.6 μg/L (4% decrease) for women in the placebo group. Serum prolactin levels increased from normal baseline levels in 32% of patients (women and men) treated with ramelteon compared with 19% of patients who received placebo.[159]

Agomelatine is a napthalenic compound with strong melatoninergic properties. It exhibits actions similar to those of melatonin, particularly on the electrical activity of SCN neurons.[160] This is in accordance with the properties of a melatoninergic agonist acting on both MT_1 and MT_2 receptors; additionally, agomelatine acts as a $5\text{-}HT_{2C}$ receptor antagonist.[161-163] Effects of agomelatine on the circadian phase[164] and on sleep have been described in humans.[139,165] PSG studies have shown that agomelatine decreases sleep-onset latency, decreases wakefulness after sleep onset and improves sleep stability (see review by Zupancic and Guilleminault[139]). The effects of agomelatine on sleep and circadian rhythms have been attributed to its agonist activity at MT_1 and MT_2 receptors.[138,139]

In subsequent studies, the parallel influence of agomelatine on the serotonergic system, initially regarded by some as an unnecessary and possibly undesirable collateral action, has been shown to have anxiolytic effects, thus conferring additional value to the drug in clinical applications,[162] particularly in the treatment of major depressive disorders.[166] These beneficial effects are mainly attributed to the blockade of $5\text{-}HT_{2C}$ receptors.[161]

5.1.3 Insomnia in Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease that is characterised by low levels of melatonin output,[167] as well as by disruptions in sleep-wake rhythms.[168] As Alzheimer's disease neuropathology progresses there is an accompanying decrease

in CSF melatonin levels.[169] Although the pattern of melatonin decrease in patients with Alzheimer's disease can be irregular,[170] the deficit can be reversed by replacement therapy. Administration of melatonin in doses ranging from 3–9 mg/day has been shown to reduce the sleep-onset time[171] and to improve sleep quality and mood in elderly individuals with dementia or mild cognitive impairment.[172] A longitudinal study carried out over a 2- to 3-year period on 14 patients with Alzheimer's disease also demonstrated that melatonin administration (6–9 mg/day) significantly improved sleep quality.[173] Several recent studies have confirmed that melatonin administration can prolong actigraphically-evaluated sleep time and decrease sleep-disruptive activity.[148,174,175]

In a larger multicentre, randomised, placebo-controlled clinical trial, two dosage formulations of oral melatonin were administered; 157 patients with Alzheimer's disease and night-time sleep disturbance were randomly assigned to one of three treatment groups for 2 months: (i) placebo; (ii) slow-release melatonin 2.5 mg/day; or (iii) melatonin 10 mg/day.[147] Melatonin facilitated sleep in a certain number of individuals, but collectively the increase in nocturnal total sleep time and reductions in awakenings 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 slow-release melatonin 2.5 mg/day group compared with placebo.[147] Indeed, large interindividual differences among patients with a neurodegenerative disease are common. It should also be taken into account that melatonin, although having some sedating and sleep latency-reducing properties, does not primarily act as a sleeping pill, but mainly as a chronobiotic.[26] Since the circadian oscillator system is obviously affected in patients with Alzheimer's disease showing severe sleep disturbances, the efficacy of melatonin should be expected to also depend on disease progression.

5.1.4 Children with Insomnia

Sleep problems are commonly noted in young children with severe learning difficulties. Symptoms including delayed sleep-onset latency, difficulty in sleep maintenance, diminished REM sleep and increased frequency of night-time waking have all been reported in various studies.[149,176] Among children with attention-deficit hyperactivity disorder (ADHD), initial insomnia has been the most commonly noted sleep disorder.[145,146,177] Nonpharmacological therapies such as sleep hygiene, behavioural interventions and relaxation techniques have been used to improve sleep disorders among children with ADHD and other disabilities.

The therapeutic potential of melatonin administration in children first attracted attention when Jan et al.[178] reported the benefits of melatonin supplementation for improving sleep in 15 children with neurological disorders. Subsequently, it was noted that children with ADHD have a delayed endogenous circadian pacemaker, as indicated by delays in sleep onset, dim light melatonin onset and time of awakening.[145,146,177] Administration of melatonin to children with ADHD resulted in significant advance of sleep onset, a reduction in sleep latency and improvement in health status.[149] A subsequent study confirmed that melatonin is effective in improving initial insomnia and increasing sleep duration in children with ADHD.[152] Furthermore, it is interesting to note that an inverted melatonin rhythm (with symptoms of melatonin secretion during the day) occurs in children with Smith-Magenis syndrome, a genetic disease caused by interstitial chromosomal deletion 17p11.2.[179] These children also experience sleep problems such as difficulty in falling asleep, shortened sleep cycles, frequent and prolonged nocturnal wakenings and excessive daytime sleepiness.[179] The time of onset of melatonin secretion in patients with Smith-Magenis syndrome is 6.00am ± 2 hours (controls 9.00pm ± 2 hours), and peak time is at 12.00 noon ± 1 hour (controls 6.00am ± 1 hour). Urinary melatonin and aMT6s levels also exhibit an inverted night/day ratio.[180] The low melatonin levels seen at night are associated with early sleep onset, frequent awakenings and early sleep offset, which are the consistent features and specific diagnostic criteria for this disease. Although the amount of melatonin secreted by Smith-Magenis syndrome patients is normal, its kinetics are erratic, with elevated secretions occurring during the day. Combination therapy based on administration of a β_1-adrenoceptor antagonist in the

morning and melatonin in the evening has been found not only to restore circadian plasma melatonin rhythmicity but also to enhance sleep and reduce behavioural disturbances.[179]

Severe learning disabilities, behavioural problems and sleep disturbances occur in tuberous sclerosis complex, another genetic disorder commonly seen in children.[181] In a randomised, double-blind, placebo-controlled study of these children, administration of melatonin 5 mg/day significantly improved total sleep time and sleep-onset latency, with no adverse effects.[182]

Another paediatric pathology in which melatonin can be useful is autism. Very low levels of endogenous melatonin are found in children with autism.[183] Recently, the long-term effectiveness of controlled-release melatonin 3 mg/day was evaluated in 25 autistic children.[184] The sleep patterns of these children were subjectively evaluated at baseline, after 1, 3 or 6 months of melatonin treatment, and 1 month after discontinuation. Following treatment, the sleep patterns of all the children studied showed improvement. Treatment gains were maintained at 12- and 24-month follow-ups and no adverse effects were reported.[184]

Reviews have concluded that melatonin is a safe, well tolerated and effective drug for treatment of sleep disorders in children with mental retardation and neurological disorders.[185] In several studies, children were monitored for periods ranging from 4 to 24 months after the initiation of melatonin treatment, with a remarkable absence of adverse effects;[184-186] however, long-term adverse effects remain to be investigated (e.g. melatonin might affect sexual maturation and reproductive function).

5.2 Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are characterised by a misalignment between the timing of the sleep-wake cycle and the environmental light/dark cycle, together with preservation of sleep mechanisms *per se*.[5] In these disorders, sleep is inappropriately aligned with the internal biological clock, and wake episodes thus occur at undesired times. Because of this, the patient experiences insomnia and excessive sleepiness during waking hours. These sleep disorders can be persistent, as seen in delayed sleep-phase syndrome, advanced sleep-phase syndrome, irregular sleep/wake pattern and periodic (non-24-hour) sleep/wake disorder, or transient, as seen in jet lag or shift work.[5] Results from animal or human studies have revealed that exogenous melatonin administration is effective in most circadian rhythm sleep disorders.[25]

5.2.1 Delayed Sleep-Phase Syndrome

Delayed sleep-phase syndrome is defined as the persistent inability to fall asleep at conventional bedtime and marked difficulty in arising in the morning, despite the occurrence of normal sleep architecture, quality and duration.[187,188] It occurs mainly in young individuals and accounts for 10% of chronic sleep disorders. Sleep onset is delayed to 3:00–6:00am, while the usual wake time in these patients is also delayed to 11:00am to 2:00pm.[188] The disorder is often misdiagnosed as sleep-onset insomnia.

It is now recognised that in patients with delayed sleep-phase syndrome the SCN has a slower running time, and that this is the main pathophysiological cause of the disorder.[189] The fact that melatonin secretion, which is controlled primarily by the SCN, is also very much delayed (to late night or early morning) in patients with delayed sleep-phase syndrome, supports the concept that the central problem in delayed sleep-phase syndrome is an abnormally long circadian periodicity.[190] An association between a polymorphism of the *AA-NAT* gene and delayed sleep-phase syndrome has been detected and it is suggested that the *AA-NAT* gene could be the susceptible gene for delayed sleep-phase syndrome.[191] Another significant finding is that 47% of patients with delayed sleep-phase syndrome are highly sensitive to light from a circadian point of view.[190]

A number of studies have demonstrated that the administration of melatonin effectively adjusts the sleep timing in patients with delayed sleep-phase syndrome.[192-196] In the earliest report, Dahlitz et al.[192] administered melatonin (5 mg/day) to eight individuals with delayed sleep-phase syndrome at 10:00pm for a period of 4 weeks and found that the treatment significantly advanced the sleep-onset time by an average of 82 minutes, with a range of 19–124 minutes. In another study, melatonin was

administered to patients with delayed sleep-phase syndrome 5 hours before dim light melatonin onset, and a significant advancement of sleep onset was noted.[193] Melatonin 5 mg/day was administered 3–4 hours before sleep onset to a group of 22 patients with delayed sleep-phase syndrome. The treatment not only significantly phase-advanced the sleep period but also decreased sleep-onset latency when compared with placebo.[196]

Recently, melatonin was used in physiological dosages (0.3 mg/day) and pharmacological dosages (3 mg/day) in the treatment of 13 patients with delayed sleep-phase syndrome.[197] The treatment was administered 1.5 hours and 6.5 hours prior to dim light melatonin onset for a 4-week period. It was found that both the physiological and pharmacological doses of melatonin advanced the circadian clock and sleep in a phase-dependent manner. The magnitude of phase advance also correlated strongly with the time of melatonin administration: the longer the administration period (number of hours) before dim light melatonin onset, the greater the effect.[197]

5.2.2 Advanced Sleep-Phase Syndrome

While insomnia is one of the most commonly reported sleep disorders associated with advancing age, elderly individuals also show other changes in sleep patterns. Some elderly patients experience persistent early evening sleep onset, and early morning awakenings, a sleep disorder known as advanced sleep-phase syndrome.[198] Sleep onset occurs at around 8:00pm and wakefulness occurs at around 3.00am. The quality of sleep is also affected as a result of increased awakenings during the night.

The disturbance of sleep/wake rhythm is attributed to attenuation of the normal rhythm of melatonin secretion, a problem that increases as individuals grow older. Other studies have provided evidence that advanced sleep-phase syndrome is an inherited sleep/wake rhythm disorder,[198-200] with some studies showing disturbances in both the sleep/wake rhythm and melatonin rhythm (as measured by dim light melatonin onset).[198] In familial advanced sleep-phase syndrome a polymorphism of the *hPer2* gene has been identified near the telomere of the chromosome 2q.[201]

The application of bright light or melatonin administration is among the chronotherapeutic procedures that have been advocated for treating this disorder. To date, melatonin has not been used in the treatment of advanced sleep-phase syndrome. Indeed, a potential conflict exists between the phase-advancing effects of melatonin and the desired phase delays in the treatment of early morning awakening, particularly in the elderly. There is evidence that bright light used early in the evening can induce a phase delay in patients with advanced sleep-phase syndrome.[202]

5.2.3 Non-24-Hour Sleep/Wake Syndrome

Non-24-hour sleep/wake disorder is commonly encountered in totally blind individuals since their sleep/wake cycles are not synchronised to the 24-hour light/dark cycle. More specifically, the circadian rhythm of sleepiness is shifted out of phase with the desired time for sleeping.[203] The most frequently reported symptoms in these patients are recurrent insomnia and daytime sleepiness. Non-24-hour sleep/wake rhythm is seen not only in the blind but also in some sighted elderly individuals.

Shibui et al.[204] administered melatonin 0.5mg at 9:00pm to a sighted individual who had been experiencing an endogenous melatonin rhythm and sleep/wake rhythm close to 25.1 hours. Following the melatonin treatment, the patient's endogenous melatonin secretion and sleep rhythms stabilised to a period of 24.1 hours. In another study[205] it was reported that administration of exogenous melatonin 0.5 mg/day for a period of 14 months stabilised a patient's sleep/wake schedule to close to 24 hours. In several blind individuals with no conscious light perception, administration of melatonin at a dosage of 3–5 mg/day was found effective not only in normalising the sleep/wake cycle[206,207] but also in reducing the variability in the timing of night sleep onset and increasing sleep duration. These studies support the value of melatonin for stabilising sleep/wake rhythm in some blind and sighted individuals who are experiencing non-24-hour sleep/wake pattern.

5.2.4 Jet Lag

The endogenous circadian rhythms of transmeridian travellers typically require several days to ad-

just to the altered day/night cycle of the new time zone to which the travellers have relocated.[208] The time taken to adapt depends on the size of the phase shift and Zeitgeber strength (photoperiod and light intensity), but it approximates to 1–1.5 hours of adaptive shift per day, with worsening of symptoms after an eastbound flight when compared with a westbound flight. Disturbed night-time sleep with impaired daytime alertness and performance are symptoms of jet lag frequently seen in intercontinental travellers.[209] Among 14 placebo-controlled field studies that examined the efficacy of melatonin treatment for alleviating the perceived jet lag associated with sleep disturbance, 11 indicated that melatonin use improved sleep quality when compared with placebo.[24] Melatonin taken during the evening at the local time of the new time zone (after a transmeridian flight) has been shown to alleviate the symptoms of jet lag, either during eastbound or westbound flights.[210,211] In a study of the effects of round-trip overseas flights on crew travellers, intake of oral melatonin 5mg at bedtime on the day of arrival and for 5 days afterward, was found to reduce sleep disturbances and symptoms of jet lag.[212] In another study, melatonin, also at a dose of 5mg, significantly improved the self-reported sleep quality and shortened sleep latency of travellers after an intercontinental flight.[213]

Administration of oral melatonin 3 mg/day, along with timely exposure to light and physical exercise, has been found to hasten the resynchronisation of a group of elite sports competitors. After a 12-hour transmeridian flight from Buenos Aires to Tokyo, the analysis of individual actograms derived from sleep log data showed that the sleep of all subjects became synchronised to the local new time within 24–48 hours.[211] More recently, a retrospective analysis of the data obtained from 134 healthy volunteers flying the Buenos Aires–Sydney transpolar route in the last 9 years was published.[26] Mean resynchronisation rate was 2.27 ± 1.1 days for eastbound flights and 2.54 ± 1.3 days for westbound flights. These findings confirm that melatonin is beneficial in situations in which realignment of the circadian clock to a new environment or to impose work-sleep schedules in inverted light/dark schedules is needed.

Whether the effect of melatonin in improving sleep is attributed to its hypnotic or chronobiotic properties is still under investigation. The available evidence suggests, however, that the observed improvements in restoration of sleep quality are attributable to both effects. Melatonin administration during the daytime may produce somnolence and fatigue,[13,93] and this potential safety risk should be taken into consideration when dealing with treatments that include daily administration of melatonin.

5.2.5 Shift-Work Disorder

Shift work is associated with a number of health problems. In the US, nearly 20% of workers are engaged in shift work, while in the UK the proportion is close to 25%.[214] Insomnia or excessive sleepiness are common complaints among shift workers. EEG studies show that night-shift workers sleep 2–4 hours/day less than control individuals,[215] with loss of stage 2 slow sleep and REM sleep.[216] Endogenous factors such as low circulating melatonin levels, increased cBT and increased circulating cortisol levels have all been hypothesised as factors that contribute to the fragmented sleep and sleep reduction seen in night shift workers.[217]

Several studies indicated that both melatonin production and sleep patterns are altered in shift workers. Roden et al.[218] found that nocturnal melatonin onset was out of phase with sleep initiation in 8 of 9 permanent shift workers. Similarly, another study noted a shift in melatonin rhythm in permanent night-shift workers.[219] An alteration of the melatonin secretion profile was seen in some shift workers, while in others it was found to be indistinguishable from those seen in day workers.[220]

Melatonin administration in doses ranging from 5mg to 10mg at bedtime after the night shift for 2–6 consecutive days improved both daytime sleep and night-time alertness in shift workers.[221,222] It was found that shift workers who took melatonin (0.5 or 3 mg/day) adapted to a shift sleep schedule more quickly than those who took placebo (56% of individuals receiving 0.5 mg/day and 73% of individuals receiving 3 mg/day).[223] It was also found that the ability to phase-shift endogenous melatonin rhythm is associated with improved shift work toler-

ance.[224] Taken together, the majority of studies of permanent night-shift workers have found melatonin to be of benefit in facilitating circadian adaptation to night-shift work. As mentioned for jet-lag applications of melatonin, the safety of daily administration of melatonin needs to be taken into consideration.

6. Adverse Effects of Melatonin

Available studies and clinical trials undertaken indicate that melatonin is a well tolerated drug for use in humans.[225,226] Only mild adverse effects such as drowsiness, headache or confusion have been reported. Fatigue occurs when melatonin is administered in the morning at higher doses (>50mg). Mild gastrointestinal disturbances such as nausea, vomiting or cramps have also been observed.[226] Indeed, most studies with melatonin point out that overall adverse effects of melatonin are insignificant and, in general, similar to those found with placebo.[227]

Melatonin treatment is remarkably well tolerated, even in very high doses and in individuals with various diseases.[26,228,229] This may not be valid for all pathologies, such as those of autoimmune etiology, because of the immunomodulatory properties of melatonin.[230] No hangover effects have been observed with melatonin when administered at reasonable concentrations, partially as a consequence of its short half-life. It must be noted that no long-term clinical studies have been conducted with melatonin as yet.

7. Conclusions

Melatonin receptors present in the SCN play an important role in the phase-shifting effects of melatonin.[6,7] The correctly timed administration of melatonin facilitates the readjustment of disrupted circadian rhythms seen after abrupt exposure to changes in the light/dark cycle schedules that are encountered in conditions such as jet lag, shift work or 24-hour sleep/wake rhythm disorders. The binding of melatonin to MT_1 and MT_2 receptors in the SCN is essential for the sleep-promoting and phase-shifting actions of melatonin. It has been suggested that changes in melatonin receptor density in the SCN are one of the main causes of circadian rhythm disturbances seen during aging and in patients with Alzheimer's disease.

Regulation of the sleep/wake cycle by the SCN is essential for the development of therapies to treat sleep/rhythm disorders. Exogenous melatonin administration possesses circadian phase-dependent hypnotic properties, and both exogenous and endogenous melatonin attenuate the circadian system's tendency to promote wakefulness.

The effectiveness of melatonin for the treatment of sleep disorders depends on a number of factors, including dosage, route of administration, (intranasal, intravenous or oral) and time of administration (day or night). Many of the recent studies on melatonin administration support the conclusion that this drug is useful in the treatment of paediatric sleep disorders. Although its mechanism is complex and not yet completely understood, melatonin as a natural regulator of sleep may be an effective therapy for treating children with neurodevelopmental disabilities. One major inconvenience is that melatonin has not obtained a regulatory approval as a drug, with the consequence that preparations sold as a food supplement do not always accomplish the necessary requirements of purity.

The newly developed drug ramelteon acts on both MT_1 and MT_2 receptors in the SCN, and is appropriately termed a chronohypnotic or chronosomnotic agent. It has been suggested that this new agent, with its novel mechanism of action, may have an important role to play in the treatment of insomnia, circadian rhythm sleep disorders, and other sleep disorders seen in children with neurodevelopmental disabilities.

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