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Melatonin rhythmicity: effect of age and Alzheimer's disease

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Abstract

The circadian rhythm of the pineal gland hormone, melatonin is generated within the hypothalamic suprachiasmatic nuclei (SCN), site of the circadian clock. The circadian clock and its output melatonin rhythm is synchronized to the 24 h day by environmental light which is transmitted from the retina to the SCN primarily via the retinohypothalamic tract. Changes in both the amplitude and timing of the melatonin rhythm have been reported with aging in humans. Whether these age-related changes (reduced melatonin amplitude, earlier timing of melatonin rhythm) are a result of aging of the retina, the SCN clock, the pineal gland, their neural connections or a combination of some or all of these is not known. The fragmented sleep/wake patterns observed in the elderly and to a greater extent in patients with Alzheimer's disease have been shown to be partly related to an altered retina-SCN-pineal axis. Therapies designed to reinforce the circadian axis (for example, administration of melatonin or light) have been reported to alleviate the disturbed circadian rhythms and disrupted sleep. Future research needs to pinpoint the site(s) of age-related dysfunction so that therapies can be specifically tailored to correct the abnormality in addition to reinforcing any of the intact processes.

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1. Introduction

The pineal gland is the major source of the hormone melatonin. In all species studied to date, there is a day/night variation in pineal melatonin production with peak concentrations occurring during the dark phase (Arendt, 1995). The melatonin rhythm is generated within the hypothalamic suprachiasmatic nuclei (SCN), site of the circadian clock. The circadian clock and its output rhythms (for example, melatonin, cortisol, core body temperature) are synchronized to the 24 h light/dark cycle by ocular light which is transmitted from the retina primarily via the retinohypothalamic tract (RHT) to the SCN. Age-related changes in melatonin rhythmicity have been reported. The age-related changes in melatonin and their possible causes will be discussed in the present review. The consequences of a dysfunctional retina-SCN-pineal axis in aging and Alzheimer's disease (AD) will also be addressed along with possible treatment strategies.

2. Age-related changes in melatonin production

Numerous studies have shown that melatonin production decreases with age in humans. Reduced concentrations have

been observed in plasma melatonin (Iguichi et al., 1982; Waldhauser et al., 1988; Ferrari et al., 2000) and urinary 6-hydroxymelatonin (Sack et al., 1986; Young et al., 1988). The major urinary metabolite of melatonin, 6-sulphatoxymelatonin (aMT6s) has also been shown to be reduced with age (Bojkowski and Arendt, 1990; Kennaway et al., 1999). Even within a fairly narrow age range (40–69 yr), we showed a significant effect of age on the daily excretion of urinary aMT6s in 160 women (Skene et al., 1990a).

Melatonin content in postmortem human pineals was also reduced with age (Skene et al., 1990b). The day/night variation in pineal melatonin content in the younger age group (18–54 yr) was not maintained in the older age group (55–92 yr) (Skene et al., 1990b). In another study of human postmortem pineal tissue, elderly subjects (61–84 yr) had lower pineal melatonin contents than younger (30–60 yr) subjects, but this difference was not statistically significant (Luboshitzky et al., 1998).

Although many reports indicate that melatonin levels decline with age, especially the nocturnal melatonin peak, some recent studies do not support a reduction (Zeitzer et al., 1999; Fourtillan et al., 2001). Under carefully controlled constant routine conditions, the melatonin rhythms in 98 young (18–30 yr) and 34 older (64–81 yr) subjects were measured. In contrast to the earlier studies, no significant difference in the amplitude of the plasma melatonin rhythms was observed. The strict selection criteria for the elderly

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subjects (healthy, disease free, non-medicated, free of alcohol, caffeine, nicotine) and the artificial conditions of the experiment (dim light, semi-recumbent, sleep deprived) may explain the discrepancy. The recent observation that the decline in melatonin production (assessed by urinary aMT6s) occurs early in life, around 20–30 yr of age may also account for the discrepant findings (Kennaway et al., 1999). The lack of effect of age (Zeitler et al., 1999; Fourtillan et al., 2001) has also been challenged by others (Cornelissen et al., 2000).

Apart from age-related changes in the night-time production of melatonin with reduced amplitude of the melatonin rhythm, whether there are age-related changes in the timing of the melatonin rhythm have been less well investigated. Field studies have demonstrated a phase advance of the melatonin rhythm in elderly compared with young women (Skene and Middleton, unpublished results). The peak time of urinary aMT6s was $3:48 \pm 26$ h/min in the older women (53–65 yr) compared to $4:47 \pm 20$ h/min in the younger women (20–30 yr). In order to assess whether these changes were independent of the subjects' sleep/wake pattern and lighting environment, Duffy and co-workers (Duffy et al., 1998) conducted a constant routine study in which factors known to affect circadian rhythms are kept constant and the subjects are sleep deprived. An advance in the peak time of plasma melatonin was still observed in the old compared to young subjects.

To date no longitudinal studies assessing melatonin rhythmicity within subjects across time have been performed. In view of the large inter-subject variation in melatonin production (Arendt, 1995), experiments of this type are needed to resolve the question of whether within an individual melatonin declines with age.

3. Possible causes of age-related changes

There are number of possible reasons for the age-related decline in melatonin production and the earlier timing of melatonin rhythm described above.

3.1. Clock related disturbance

Melatonin rhythms may be disrupted because there is global neurodegeneration with aging which includes the SCN, site of the human circadian clock (Swaab et al., 1985). The observed changes in the melatonin rhythm (reduced amplitude, earlier timing) may reflect a general disturbance of all SCN-driven circadian rhythms, e.g. core body temperature, cortisol. In addition to melatonin, age-related changes in the amplitude of other circadian rhythms have also been reported, e.g. core body temperature (Carrier et al., 1996; Dijk et al., 2000). The earlier timing of the melatonin rhythm observed in old subjects was mirrored by earlier timing of the core body temperature rhythm (Duffy et al.,

1998). These findings suggest that the changes observed in the melatonin rhythm may be part of a general effect of aging on the clock and/or its regulation.

One of the reasons for a phase advance of circadian rhythms could be an age-related change in circadian period (τ). Early temporal isolation experiments suggested an inverse relationship between the period of the clock and the age of the individual. In addition, 80% of subjects in the 50–80 yr range showed a spontaneous internal desynchronization of rhythms that may affect sleep patterns and other aspects of biological aging (Weitzman et al., 1982; Mirmiran et al., 1992). However, both in forced desynchrony experiments (Czeisler et al., 1999) and in totally blind free-running subjects (Lockley and Skene, unpublished results), no age-related change in period (τ) has been observed. These findings are in contrast to a report describing a lengthening of period in six totally blind subjects of 40–50 yr of age (Kendall et al., 2001). Further research with an increased number of subjects is needed to resolve this issue of age-related changes in period (τ).

Specific age-related rhythm changes have also been noted in the human SCN. The circadian and circannual fluctuations in vasopressin-expressing neuron numbers in the SCN decreased during aging (Hofman and Swaab, 1994, 1995). The marked diurnal oscillation in the number of vasopressin-expressing neurons in the SCN of young subjects disappeared in subjects over the age of 50 (Hofman and Swaab, 1994). Whereas in young subjects low vasopressin neuron numbers were found during the summer, and peak values in autumn, the SCN of people over 50 yr of age showed a disruption of the annual cycle with a reduced amplitude (Hofman and Swaab, 1995). How these changes within the SCN translate into the observed changes in circadian rhythmicity is not yet known.

3.2. Abnormalities in entrainment

Alternatively the neural processes involved in entrainment (synchronization) of the clock may be dysfunctional or sub-sensitive. For example, there may be a weakened link to the SCN pacemaker with any part of the photic input pathway (retina-RHT-SCN) being dysfunctional. Reduced light transmission through the ocular lens or a defective retina-RHT-SCN pathway are possible causes of disturbed circadian rhythms in aging (and in AD). Cataract and maculopathy are more common in the elderly (Meisami, 1988). With aging there is a progressive decline in the capacity of the lens to transmit short wavelength light (Lutze and Bresnick, 1991) and a reduction in short wavelength S-cone sensitivity (Suzuki et al., 1998). Recent reports have demonstrated the existence of a novel short wavelength photopigment in the human retina (Brainard et al., 2001; Thapan et al., 2001). This non-rod, non-cone photoreceptor system has been shown to mediate the light-induced suppression of nocturnal melatonin. This finding showing that the human circadian–pineal axis is selectively

sensitive to short wavelength light suggests a link between the aging eye, reduced transmission of short wavelength light and weakened photic entrainment of the circadian clock. If proven, exposure to short wavelength light would be expected to facilitate circadian rhythm entrainment and synchronize the disturbed circadian rhythms and sleep disorders observed in the elderly. Studies of this sort are currently underway.

3.3. *Insufficient zeitgebers*

Although early research showed that nonphotic time cues (*zeitgebers*) were important in the synchronization of the endogenous clock, more recent research has shown that environmental light is the major time cue in entrainment of the human circadian system. The importance of ocular light as a temporal cue has been very clearly demonstrated in circadian studies of blind subjects (Lockley et al., 1997a). Blind subjects with no light perception and in particular those who have been bilaterally enucleated show desynchronized (free running non 24 h) circadian rhythms including melatonin and cortisol (Lockley et al., 1997a; Skene et al., 1999).

Reduced *zeitgeber* strength could be a result of environmental factors. For example, there is evidence to suggest that elderly people are exposed to reduced illumination levels in their daily lives (Campbell et al., 1988; Van Someren et al., 1997; Shochat et al., 2000; Mishima et al., 2001). Some studies have shown an inverse relationship between light intensity and sleep disturbances in the elderly (Shochat et al., 2000; Mishima et al., 2001). Higher light levels predicted fewer night-time awakenings and severe dementia predicted more daytime sleep and lower mean activity (Shochat et al., 2000).

In older people there appears to be a maintained responsiveness of the circadian pacemaker to light (Klerman et al., 2001), which implies that scheduled bright light exposure could be used to treat circadian phase disturbances and related sleep problems in older people. Supplementary exposure to midday bright light significantly increased melatonin secretion to levels similar to those in young adults (Mishima et al., 2001).

3.4. *Pineal gland dysfunction*

The pineal gland itself may display age-related changes. For example, the incidence of concretions in the pineal increases with age (Humbert and Pevet, 1991), which may explain the decline in melatonin production with age (Kunz et al., 1999). The size of the pineal calcification appears not to be associated with melatonin secretion (Bojkowski and Arendt, 1990). However, an approximation of the size of the uncalcified pineal tissue, presumably representing active pinealocytes, has been reported to associate positively with the total 24 h urinary aMT6s excretion (Kunz et al., 1999). Calcification of pinealocytes is considered to result from

death or degeneration of the cell itself, thus leading to an overall decrease of pineal activity (Kunz et al., 1999). Puig-Domingo et al., (1992) supports an alternative view that pineal calcification is a result of hyperactivity of the pineal and not a sign of inactivity or atrophy.

4. Alzheimer's disease (AD)

The fragmented sleep-wake pattern which occurs in senescence is even more pronounced in AD (Witting et al., 1990; Mirmiran et al., 1992; Bliwise et al., 1995; Ancoli-Israel et al., 1997). Demented patients frequently suffer from sundowning, characterized by an exacerbation of symptoms indicating increased arousal in the late afternoon, evening or night. Sundowning is considered to be a chronobiological disturbance (Lebert et al., 1996) related to a phase delay of body temperature caused by AD (Volicer et al., 2001). Sleep disruption of the caregiver caused by nocturnal problems of demented patients is the primary reason for nursing home placement rather than cognitive impairment (Pollak and Perlick, 1991).

In AD, disruptions of the circadian rhythms are often so severe that they are even thought to contribute to mental decline (Moe et al., 1995). In AD patients with disturbed sleep-wake rhythms there is also a higher degree of irregularities in melatonin secretion (Mishima et al., 1999). An impairment of melatonin secretion is present that is related to both age and severity of mental impairment. The nocturnal growth hormone secretion and both the mean levels and nadir values of plasma cortisol are also related to mental impairments (Magri et al., 1997). Mishima et al., (1997) claim that AD patients have an intact body temperature rhythm, in agreement with Touitou et al., (1997) and an earlier study of Prinz et al., (1984), while multi-infarct dementia patients have a low amplitude and disorganized pattern of body temperature. This was in marked contrast to the disturbed rest-activity rhythm in both groups. Rest-activity rhythm disturbances and temperature rhythm disturbances may thus have a different pathological basis, but it should be noted that no neuropathological confirmation of the different types of dementia was available in that study. In addition, a substantial proportion of both nursing home residents with night time incontinence and frail geriatric patients experience a reversal of the normal diurnal pattern of urine excretion (Ouslander et al., 1998). The circadian rhythm in blood pressure has been reported to be preserved in the early stages of AD, but is disrupted in advanced or institutionalized patients (Cugini et al., 1999).

4.1. *Pineal changes*

A number of studies have shown that melatonin levels are lower in AD patients compared with aged matched controls

(Skene et al., 1990a,b; Uchida et al., 1996; Liu et al., 1999; Mishima et al., 1999; Ohashi et al., 1999; Ferrari et al., 2000). In patients who lack serum melatonin rhythms, clinical symptoms of delirium and sleep-wake disturbance were frequently but not always observed (Uchida et al., 1996). In AD patients with disturbed sleep-wake rhythms a higher degree of irregularities in melatonin secretion have been observed (Mishima et al., 1999). Our finding that the daily variations in pineal melatonin and 5-methoxytryptophol content disappeared in AD patients (Skene et al., 1990a,b) may be linked with the clinical observations of sleep disorders and sundowning in these patients. Others have reported that there is a selective impairment of the nocturnal melatonin peak in dementia (Ferrari et al., 2000) or that the melatonin levels are increased in AD patients during daytime and that these patients do not react to bright light (Ohashi et al., 1999). Thus an impairment of melatonin secretion is present that is related to both age and severity of mental impairment.

Although AD patients appear to have diminished pineal function, no evidence has been observed in this structure of neurofibrillary tangles, the accumulation of neurofilaments, tau, hyperphosphorylated tau (stained by Alz-50) or β /A4 amyloid deposition in pinealocytes (Pardo et al., 1990). Thus although decreased melatonin levels may indicate decreased functioning of pinealocytes in AD, this is not accompanied by typical neuropathological AD changes of the intrinsic cells or afferent fibers (Pardo et al., 1990).

4.2. SCN changes

The above findings could also suggest that the neurodegenerative process in AD affects the SCN pacemaker which, in turn, affects melatonin rhythmicity. For example there may be a specific lesion associated with the SCN in some AD subjects. There are reports that the expression of vasopressin is preferentially lost from the SCN in AD (Liu et al., 2000) and that light therapy prevents the age-related loss of vasopressin expressing neurons in the rat (Lucassen et al., 1995). The SCN of AD patients have pretangles (van de Nes et al., 1998) and tangles (Stopa et al., 1999) indicating that the SCN is affected by AD. However, diffuse amyloid plaques are only seldom noted in this nucleus (van de Nes et al., 1998; Stopa et al., 1999). In AD there was a marked decrease in the number of vasopressin-expressing neurons in the SCN which occurred at an earlier age and was more dramatic than in non-AD patients (Swaab et al., 1985, 1987). Stopa et al. (Stopa et al., 1999) found a decrease in the density of vasopressin and neurotensin neurons as well as a corresponding increase in the GFAP stained astrocytes in AD patients. The immunocytochemical data indicating decreased activity of the SCN in AD have been confirmed by *in situ* hybridization. The total amount of vasopressin-mRNA was three times lower in AD than in age- and sex-matched controls. In controls the amount of vasopressin mRNA was more than three times higher during the day than at night, whereas no clear diurnal rhythm of

vasopressin mRNA was observed in AD patients (Liu et al., 2000). The data mentioned above support the idea that damage to the SCN may be the underlying anatomical substrate for the disturbances in circadian rhythmicity observed in Alzheimer's disease.

In a recent study (Harper et al., 2001), circadian differences were observed between AD subjects and those with frontotemporal degenerative dementias (FTD): in FTD, core body temperature and rest-activity patterns were compromised whereas in AD both central pacemaker and behavioral expression were altered.

4.3. Retina

Apart from the age-related changes in ocular processing discussed above, there are some specific changes noted in AD. Age-related maculopathy is associated with AD (Klaver et al., 1999). Not only the retina but also the optic nerve, which provides direct and indirect light input to the SCN, show degenerative changes in AD (Hinton et al., 1986; Katz et al., 1989; Trick et al., 1989; Blanks et al., 1996a,b). In the macula of AD patients retinal cell degeneration has been observed without neurofibrillary tangles, neuritic plaques or amyloid angiopathy being present in the retina or optic nerves (Blanks et al., 1989, 1996a,b). Extensive neuronal loss (36%) was reported throughout the entire retina of AD patients, but being most pronounced in the superior and inferior quadrants. The ratio of astrocytes to neurons is significantly higher in AD (Blanks et al., 1996a,b), indicating that a process of neurodegeneration takes place.

On the other hand, there are also a number of observations suggesting that visual deficits in AD do not stem from neuroretinal dysfunction. Although earlier work showed a higher proportion of abnormalities in the retinal nerve fiber layer of AD patients than in controls (Hedges et al., 1996) by scanning laser polarimetry the retinal nerve fiber layer thickness was not altered in the earlier stages of AD (Kergoat et al., 2001). In contrast to the observed degenerative changes mentioned above, in another study (Curcio and Drucker, 1993) the reduced density of retinal ganglion cells in AD patients was found to be similar to that of aged controls, and myelinated axon number in the optic nerve of AD patients was found to be unaffected in another report (Davies et al., 1995). Moreover, the nerve cells located more distally in the retina give rise to electrical signals in early and moderate Alzheimer patients that are not different from those in controls (Justino et al., 2001). Future studies need to resolve these discrepancies in the literature on retinal and optic nerve degeneration in AD in order to make clear whether both the input of the visual system to the SCN and the SCN itself are affected in AD.

4.4. Consequences of disturbed circadian rhythms in aging and AD

Disturbed circadian rhythms are frequently associated with a reduction in nighttime sleep quality and duration, a decrease in daytime alertness, an increase in daytime napping and an attenuation in cognitive performance (Myers and Badia, 1995; Lockley et al., 1997b). In the elderly disordered sleep architecture is found with reduced time spent in slow wave sleep (SWS) and in rapid eye movement (REM) sleep (Klerman et al., 2001). Aging is also frequently associated with complaints about earlier bed and wake times. These changes in sleep timing appear to be associated with an earlier timing of endogenous rhythms, including core body temperature and plasma melatonin (Duffy et al., 1998).

4.5. Possible treatment strategies

Nighttime insomnia and nocturnal wandering in AD patients often poses unbearable problems for caregivers. Hypnotic or antipsychotic medications are only minimally effective (Witting et al., 1990; van Someren et al., 1993; Dowling, 1996; Harper et al., 2001). Benzodiazepines have minimal effects on sundowning (Burney-Puckett, 1996), while sleep-wake cycle disturbances may even be aggravated by a classic neuroleptic like haloperidol (Wirz-Justice et al., 2000).

Despite the reported changes in the retina-SCN-pineal pathway described above, the precise site(s) of dysfunction in aging and AD are not known. To date ‘chronobiotic’ strategies designed to reinforce the photic and nonphotic entraining signals, namely light and melatonin have been assessed.

4.6. Melatonin

There are preliminary reports that melatonin decreases sundowning in AD patients (Brusco et al., 1998, 1999). A significant decrease in agitated behaviors and confusion in the evening hours, or ‘sundowning’ has been seen following melatonin administration (Cohen-Mansfield et al., 2000). In addition to melatonin’s ability to phase shift circadian rhythms (Deacon et al., 1994), in *in vitro* experiments melatonin was found to function as an antioxidant and neuroprotector in rat and primate brain tissue (Pappolla et al., 2000; Reiter et al., 2000; Tan et al., 2000). Melatonin has also been reported to protect neurones against β -amyloid toxicity (Pappolla et al., 1997, 1998), to prevent β -amyloid-induced lipid peroxidation (Daniels et al., 1998) and to alter the metabolism of the β -amyloid precursor protein (Song and Lahiri, 1997). The decreased levels of melatonin in AD may thus be involved in the pathogenesis of AD. However, this remains to be proven.

4.7. Light therapy

Successful attempts have been made to control both the disturbed pattern of sleep and wakefulness and behavioral disturbance in patients with dementia using ‘white light therapy’ (Satlin et al., 1992; Mishima et al., 1994; Campbell et al., 1995; Colenda et al., 1997; Van Someren et al., 1997, 1999; Yamadera et al., 2000). The latter study also showed an improved mini-mental state examination score, especially of the early stages of AD. Bright light therapy not only improved circadian rhythms but also the cognitive state of these AD patients (Yamadera et al., 2000). The recent finding that short wavelength light is more effective at suppressing melatonin than long wavelength light (Brainard et al., 2001; Thapan et al., 2001) suggests that adjusting the spectral composition of light may improve the effectiveness of light therapy. Our recent preliminary data showing blue light to be more effective than white light at phase shifting melatonin rhythms (Warman et al., unpublished results) supports this idea. More research in this area is needed.

The above observations indicate that resetting of the circadian system by non-pharmacological means may have important therapeutic consequences for AD patients. It also shows that there is still plasticity in neuronal systems of aged individuals, even if they suffer from AD.

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