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CLINICAL REVIEW

Managing jet lag: Some of the problems and possible new solutions

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S U M M A R Y

Jet lag is due to the misalignment of the internal circadian clock(s) with external time cues. For short stopovers (1–2 days) adapting the circadian system is not advised, and at present immediate circadian adaptation is virtually impossible. The use of short-term measures such as judicious naps, caffeine and short acting hypnotics to maintain alertness and sleep is preferred. For intermediate length stays (3–5 days) a phase position with the circadian nadir situated within the sleep period is desirable but difficult to achieve. For longer stays (more than 4–5 days) strategies to hasten adaptation include timed exposure to and avoidance of light. The use of artificial light enriched with short wavelengths may be beneficial. The American Academy of Sleep Medicine recommends the timed use of the chronobiotic melatonin to hasten adaptation. Large individual differences in rate and direction of adaptation make timing treatment according to individual circadian phase difficult. Individual differences in tolerance to the sleep deprivation of jet lag may relate to a length polymorphism in the human clock gene *PER3*. The maximum efficacy for jet lag avoidance is by pre-flight adaptation, however, this requires time and commitment.

Introduction

In the last few years at least 15 reviews have addressed this subject or the broader subject of circadian rhythm sleep disorders.[1–15] Rather than repeating this exercise the present review, after an introduction and summary, will consider problems of effective treatment and potential future means of managing jet lag.

Jet lag has never been completely defined, although anyone who has suffered from this problem has no difficulty in identifying their personal symptoms. It is formally described as circadian desynchrony, or a mismatch between the timing of the internal circadian (circa 24 h) clock(s) and the external environment. After an abrupt shift in time cues such as after time zone change the circadian system adapts slowly to realign with the new schedule, approximately one day for each hour of time zone change, faster westwards, with different components of the system adapting at different rates (internal desynchrony).[5]

The perceived manifestations are variable from one individual to another, with number of time zones crossed, with direction and timing of flights and probably with seasons. However, the major complaints are poor sleep, daytime fatigue and poor performance.[15,16] Travelling eastwards, short sleep and long sleep latency are common, travelling westward short sleep and early wake up are manifest. Poor alertness and fatigue during daytime are attributed partly to sleep deprivation and partly to the concomitant presence of night time rhythm physiology – the nadir of the core body temperature, alertness, performance, metabolism and the peak of melatonin secretion. In this Olympic year of 2008 with many athletes travelling over large numbers of time zones to Beijing, the question of physical performance has been addressed in some detail.[3,5,8] One of the earliest descriptions of the effects of jet lag on physical performance concerned American baseball players who performed significantly worse when playing away over an eastward time zone transition.[17]

There are possible long term consequences of frequent desynchrony as evidenced by epidemiological and animal studies.[18–21] These include cognitive deficits, gastrointestinal problems, increased risk of cancer, infertility and heart disease. However, not all reports are consistent. Adapting to phase shift becomes harder as we grow older for uncertain reasons.[22,23]

Circadian timing system

We are a diurnal species: human physiology and behaviour are normally aligned with the 24 h day such that we are alert and active during the daylight hours and asleep during the dark phase of the day. Evidently social and work constraints can impose other behavioural arrangements: shift work is the primary example and many of the problems of jet lag are common to shift work. However, for most people jet lag symptoms resolve in time as the circadian system adapts to the new time cues, whereas rotating shift work schedules lead to frequent desynchrony with symptoms which persist, and also become worse with age.

The underlying basis of our diurnal behaviour resides in the circadian timing system.[24,25] Circadian (approximately 24 h) rhythms

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Nomenclature

Chronobiotic A substance that adjusts the timing of internal biological rhythms, or more specifically a substance that adjusts the timing of the central biological clock.

Acrophase The time of the peak of a rhythm, usually the peak time of the best-fitting mathematical function approximating the data.

Amplitude The amount of variability due to a given rhythm, usually defined as equal to one-half the peak to- trough difference

Circadian Occurring or recurring about (latin-circa) once per day (diem). Biological circadian rhythms are internally generated and, in humans, have a period which is usually slightly longer than 24 h, other terms include circannual: about 1 year, ultradian or pulsatile: with a period shorter than 20 h.

Period The duration of one complete cycle of a rhythmic variation, also known as tau (t).

Phase A distinct stage in a process of change, in this case a circadian rhythm.

Synchronizer, time cue or zeitgeber A periodic stimulus capable of determining the timing, with respect to clock hour or calendar date, of a given endogenous rhythm. A synchronised rhythm having the period of a specific time cue (24 h) does not necessarily have the 'correct' phase, e.g., melatonin peak production at night. An 'entrained' rhythm is synchronised with the correct phase.

are internally generated and by definition they persist in the absence of time cues such as alternating light and darkness. Individuals kept in a time free environment (or at least with very weak time cues), manifest their own endogenous periodicity – 'free-running', an inherited characteristic. On average human endogenous period (or tau) is about 24.2 h according to controlled experiments[26,27] although this does depend on previous experience of time cues.[28] A short tau is associated with morning diurnal preference (larks) and a long tau with evening preference (owls) in a normally entrained environment.[29] Whilst probably every cell in the body possesses a self-sustaining oscillator(s) or clock(s), this symphony of oscillators is coordinated by the central circadian pacemaker situated in the supra-chiasmatic nuclei (SCN) of the hypothalamus.[24] Removal of the SCN in mammals leads to the loss of virtually all circadian rhythms, and the SCN itself shows long term self-sustained oscillations of circa 24 h in metabolism and electrical activity in vitro.[30,31]

The mechanism of circadian rhythm generation has been the subject of intense research activity in the last few years. The basis is a negative feedback loop of clock gene expression.[24,25] Various polymorphisms have been identified in human clock genes and associations are evident with phenotypic characteristics such as diurnal preference, vulnerability to disease and probably rate of adaptation to phase shift.[32–36]

Resetting human circadian rhythms

Because human tau is not exactly 24 h the circadian system has to be reset daily or at least frequently in order to maintain 24 h clock time. For a tau of, e.g., 24.5 h the timing must be advanced by 0.5 h per day and for a tau of 23.5 h it must be delayed by 0.5 h per day. The factors which synchronise/entrain or reset the clock are known as zeitgebers (time-givers or time cues). The most important by far is the alternation of light and darkness. Blind people with no perception of light frequently show free-running circadian rhythms and oscillate into and out of phase with 24 h clock time for their entire lifetime unless a synchronising treatment is employed and is effective.[37–41] In rare blind subjects with no conscious light perception, circadian photoreception and light entrainment are possible via an intact retino-hypothalamic tract.[42] Other zeitgebers include scheduled sleep and activity, hard exercise, meal timing,[5] and some pharmacological treatments such as the hormone melatonin.[10]

All zeitgebers modify clock timing according to a phase response curve. This simply means that the direction and magnitude of the shift in a given rhythm are dependent on the time the stimulus is applied. For example, light in the 'biological' early morning will advance the circadian system whereas light in the late biological evening will delay the circadian system. The cross over point between advances and delays is close to the core temperature minimum and the melatonin maximum and the largest shifts are found close to this point[43,44] (Fig. 1). 'Biological night' is often defined as the time during which the hormone melatonin is secreted.[45] After an 8–12 h time zone change 'biological night' will be situated precisely during the day.

The pathway by which light affects the clock has also been intensively investigated recently.[46–50] The primary neural input to the SCN is the retino-hypothalamic projection. Circadian photoreception is possible in the absence of rods and cones, via specialised light sensitive retinal ganglion cells projecting directly to the SCN and which use a novel opsin–melanopsin – which is preferentially sensitive to short wavelength light (460–480 nm). In normal circumstances (i.e., with an

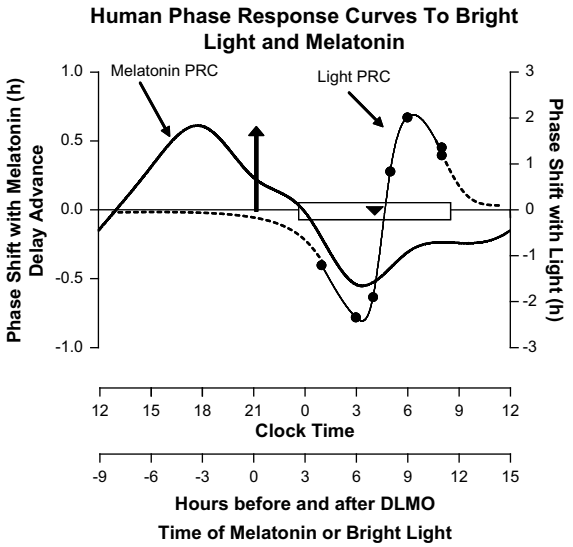

Fig. 1. This light PRC was generated from 7 subjects who free-ran through about 3 days (73.5 h) of an ultradian LD cycle (2.5 h wake in dim light <100 lux alternating with 1.5 h sleep in dark) (Eastman and Burgess, unpublished data). Subjects lived on the ultradian schedule on 2 different occasions, once with bright light pulses, about 3500 lux, for 2 h at the same time each day, and once without bright light pulses, counterbalanced. Phase shifts of the midpoint of the melatonin rhythm collected in dim light (<5 lux) before and after the 3 days were plotted against the time of the light pulse relative to each subject's baseline DLMO (Dim Light Melatonin Onset)[55] and corrected for the free run when the bright light was not applied. Upward arrow: average baseline DLMO, rectangle: average baseline sleep schedule, triangle: estimated time of T_{min} (DLMO + 7 h). The solid line is a smoothed curve fit to the 7 points. The melatonin PRC was calculated from the data of Lewy et al.[55] Subjects ($n = 6$), living at home, took 0.5 mg melatonin at the same time each day for 4 days. Phase shifts of the DLMO were plotted against the time of melatonin administration relative to each subject's baseline DLMO. A smoothed curve was fit to the data after averaging the 70 data points into 3 h bins. From: Revell VL, Eastman CI. How to trick mother nature into letting you fly around or stay up all night. J Biol Rhythms 2005 Aug;20(4):353–65, by permission.

intact visual system) rods, cones and ganglion cells all participate in relaying photic information to the SCN.

The direction and speed of shift of the circadian system to adapt to an abrupt change of time cues is dependent to a large extent on the exposure of an individual to ambient light: timing, intensity and probably spectral composition of light are critical.

Individual variability when adapting to phase shift/time zone change

The faster the circadian system adapts to the new time zone the shorter the symptomatic period. Thus hastening adaptation is a primary goal. If it were possible to predict the precise times of exposure to specific zeitgebers such as light and/or melatonin for an individual subject and journey, and if compliance were complete, we should be close to resolving the problem. The use of all available time cues theoretically will have the greatest efficacy. Light exposure during biological night will improve alertness and hasten adaptation if correctly timed.[44,51,52] Concomitant suppression of endogenous melatonin may contribute to the resetting effects of light. Melatonin during biological day will increase sleep propensity[53,54] and will likewise hasten adaptation when correctly timed: the PRC to melatonin is approximately the reverse of that to light.[10,44,55] Most other jet lag treatments involve pharmacologically maintained alertness, the use of hypnotics for sleep and scheduling of activities, meals and light exposure/avoidance to appropriate times. It is of interest to note that possibly the most ancient advice given to time zone travellers was to time their behaviour, meals, etc., to be in synchrony with the new time zone as soon as possible. Notably the clock in the liver adapts more rapidly than the central circadian pacemaker[56] to abrupt phase shift, at least in rats, and scheduled sleep itself contributes to light avoidance and enhanced phase shift, thereby confirming the utility of this advice.[57]

Numerous attempts have been made to generate instructions as to timing of light exposure and (equally important) light avoidance after landing at destination. See, for example, Midnight Sun.[58] Likewise timed treatment with melatonin as a chronobiotic has received much attention (see cited reviews). There is little substantial evidence for the efficacy of light exposure and avoidance after landing, probably because of the difficulties of avoiding inappropriate natural bright light.[59] Meta-analyses of the efficacy of melatonin disagree although most publications report beneficial effects in spite of inappropriate timing in some cases.[60–62] The American Academy of Sleep Medicine has recommended the use of melatonin for jet lag.[63] However, all general instructions assume an average phase, direction and rate of adaptation to time zone change. In fact there are enormous individual differences, even in relatively controlled experiments. These were originally reported many years ago[23,64–66] with core body temperature as the usual marker rhythm. Recently the melatonin metabolite 6-sulphatoxymelatonin has proved to be the best rhythm marker in field studies since it is less distorted by factors such as meals, exercise and sleep (less 'masked') than other markers.[67–70]

In the first field experiment on alleviation of jet lag by melatonin,[71,72] using this marker, together with urinary free cortisol, 1 of 7 placebo treated subjects adapted by delay to an eastward time zone transition (8 h) whereas the others adapted by advance. In a controlled laboratory simulation of abrupt 9 h advance time zone change, Samel and co-workers[65] found that 3 of 8 subjects adapted eastward by delay and the others by advance. Deacon and Arendt[73] in a simulated jet lag study found that even with subjects carefully synchronised before abrupt phase shift, 2 of 7 subjects delayed to an advance 9 h shift. Spencer et al[74] reported that 5 subjects travelling over 10 time zones eastward delayed and 4 advanced. In addition to the variable direction of adaptation variable speed of adaptation in either direction was evident in all these examples.

Most recently, observing adaptation to an abrupt change of shift work schedule of 12 h, Gibbs et al[75] found that 6 of 19 subjects delayed, 6 advanced and 7 hardly changed phase for a week after the schedule change. The response was at least partly predictable on the basis of initial circadian timing such that early phase people advanced, late phase people delayed and intermediate types were stuck in limbo whereby probably the circadian timing was such that morning light and evening light counteracted each other's phase shifting effects to maintain a persistent state of desynchrony. This situation is likely to occur after large time zone transitions. It suggests that strict maintenance of dim light ($<$10 lux) either during biological morning or biological evening in the new time zone will facilitate adaptation.

Bright light applied very close to the core body temperature minimum in laboratory studies can lead to large phase jumps of the circadian system.[76] Moreover melatonin treatment close to the body temperature maximum can split sleep into 2 components which migrate in different directions (advance and delay) in free running conditions.[77] Both of these situations might lead to very rapid phase adjustment, however, the responses whilst striking, were rather unpredictable and thus unsuitable for general application. Natural bright light exposure at critical times has anecdotally (and rarely) been observed to associate with suppressed amplitude (of melatonin) and rapid phase adjustment in shift workers (Gibbs, Hampton, Morgan, Arendt, unpublished observations) and this phenomenon may in some cases lead to unpredictable rapid adjustment to time zone change.

Evidently instructions as to the use of light/chronobiotic treatments predicated on a homogeneous response to a particular shift will be compromised by this variability. Thus knowledge of the likely direction of shift for each individual, and control of light exposure, would no doubt improve the consistency of treatment efficacy. This ideal situation would require the use of rapid assessments of phase prior to treatment. A normal environment phase can to some extent be estimated using normal wake up times (which are usually about 1–2 h after body temperature minimum). However, following time zone change and before full adaptation has occurred, phase is a moveable feast with different individual responses being so variable. Thus treatment timing can be fairly precisely defined in an entrained individual but not in a subject who is partly or completely out of phase. The prime examples of such subjects are long haul pilots who constantly are subjected to abrupt changes of time zone and hence local time cues.

It is possible that genetic variables may help predict response to phase shift and also the severity of symptoms (see later).

Instant evaluation of phase remains a pipe dream, however, various practical approaches to this problem may include a biosensor for measurement of the rise and fall of melatonin secretion (provided that this is not suppressed by light) thus defining biological night. If biological night-time is known, correct timing of light or chronobiotics to induce a particular shift can be predicted.

One of the more interesting features of the use of melatonin is that it apparently influences the direction of shift when pre-flight treatment is employed,[65] and can at least partially counter the effects of conflicting bright light exposure.[78]

Current strategies to manage jet lag

Whether to aid adaptation or not depends on the length of time to be spent in the destination time zone. For short stop-overs (e.g., business trips for a day or 2) there is little point in provoking adaptation as subjects will not be completely adapted whatever the approach and will be at least partly out of synchrony when returning home. Advice is to obtain sleep and alertness by whatever means and to schedule important meetings at times of maximum alertness in the departure time zone. Naps, short acting hypnotics and stimulants,

e.g., caffeine have their place in this scenario.[15] Most recently the anti-narcolepsy drug modafinil has been registered for use in shift work sleep disorder[79] and although no data address its use in jet lag the similarity between these situations of desynchrony suggest that it may be useful for maintained daytime alertness.

For intermediate length of stop-overs the advice is not solid. In the author's opinion, it should be possible to induce a small shift such that body temperature minimum and melatonin maximum occur just during scheduled sleep time. In principle this should be helpful to sleep and alertness and not greatly compromise readaptation back to departure time zone. This scenario has been recommended for shift workers[44,80] and would correspond, for example, to maintaining body clock time somewhere in the mid-Atlantic ocean for travel to the eastern USA.

For stays of more than 4–5 days circadian adaptation is desirable. With no specific treatment it is possible to maximise the likelihood of rapid adaptation in the shortest direction by judicious light avoidance and exposure on the plane. For example, when travelling westward, light through the cabin window during departure evening time and light avoidance during the second half of departure night and early morning will in principle help initiate the desirable phase delay. When travelling eastward, light exposure during departure early morning will help initiate a phase advance. Light avoidance during departure evening and the first half of the night will avoid perceiving light at the wrong time, i.e., in a phase delaying position. Similarly melatonin taken pre-flight during departure late afternoon/early evening will help initiate a phase advance (as suggested by laboratory experiments and at least one field study[15,44,10,65,71]). Taken during departure early morning it should help initiate a phase delay[55] although no field data address this possibility to the author's knowledge.

It is possible, although there is no published evidence to support this contention, that extreme evening types will find it easier with appropriate light exposure and chronobiotic treatment to delay to a large eastward transition than to advance.

For very large time zone changes (10–12 h) it is possible anecdotally to split sleep into the period post-lunch in the departure time zone and the night period in the destination time zone. There is no data to support this approach but it makes use of the 2 periods of natural sleep propensity during the 24 h day.[81]

The most important factor in adapting to time zone change is to preserve sleep. It is of course possible to sleep out of phase with the circadian system although sleep will be compromised.[82] Sleep in the main cabin of a long haul flight is likely to be fragmented to say the least. The design of seats, the angle of recline, the light environment of the cabin all play a role. Meals presented in the middle of biological night are undesirable (increased risk factors for heart disease ensue[83] and are best avoided). Hydration with water not alcohol, is recommended in the dry air of the aircraft cabin. Travelling business or first class has great advantages in terms of sleeping conditions, however, the expense involved means that this solution is only for the few.

It is important if possible to sleep during destination night-time and to this end short acting hypnotics have been used with some success[14] (see other cited reviews[5]). Although they do not greatly influence circadian adaptation it is obviously possible to combine pharmacologically induced sleep with appropriate exposure to zeitgebers (natural and pharmacological) pre-flight and on arrival.

There is only one sure fire way of avoiding jet lag altogether and that is to adapt to the new time zone before flight. There are various ways of accomplishing this but all involve time and commitment. For example, we[73] were able to shift a group of subjects in semi-controlled conditions by 9 h westwards simply by exposing subjects to circa 1000 lux broad spectrum white light for 9 h daily, delaying this exposure 3 h per day for 3 days then maintaining the new schedule for 2 days at 9 h west. With the exception of the light exposure times, subjects were free to continue their normal activities. We achieved a steady homogeneous shift of core body temperature, the melatonin rhythm (as 6-sulphatoxymelatonin) and sleep with no ill effects except a small suppression of endogenous melatonin production during light treatment. Similar data using such a 'nudging' technique with light have been reported by Stewart et al. and used for the preparation of astronauts for space flight with sleep and alertness arranged for a particular circadian phase.[84] This latter group have moreover used a combination of light and melatonin to shift the circadian system eastwards pre-flight by circa 3 h[85] (Fig. 2).

These techniques, particularly the eastward pre-flight shift, require careful compliance, avoidance of inappropriate light, zero evening social life pre-flight and no last minute packing the evening before departure. A slow pre-flight adjustment avoids any deleterious effects of desynchrony.[83] Intermittent light exposure works as well as continuous exposure[85] thus there is some flexibility in activities during light treatment. However, it is important to induce a shift pre-flight which is sufficiently large as to avoid morning light in the new time zone falling before core temperature

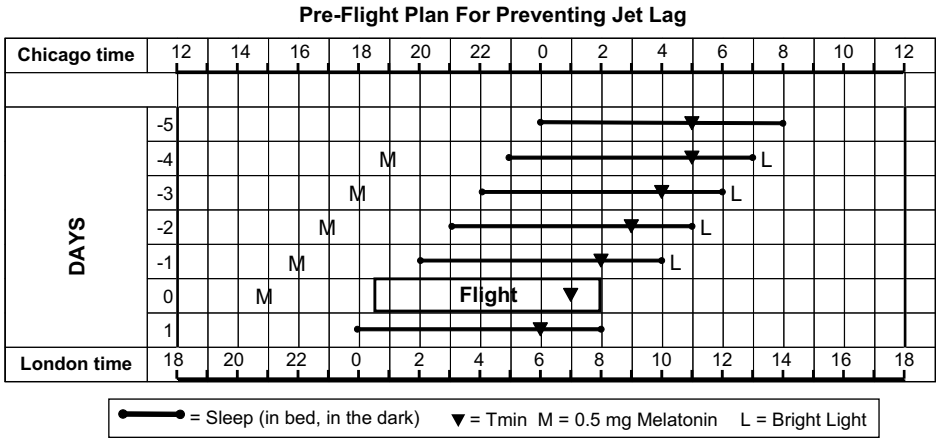

Fig. 2. Pre-flight schedule to advance circadian rhythms before an eastward flight across 6 time zones. Day −5 shows the sleep schedule and T_{min} of a typical young person. On day −4, 0.5 mg melatonin is taken 5 h before baseline bedtime and intermittent bright light pulses are used upon wakening, both timed to phase advance. Each day the schedule is advanced by 1 h, to keep up with the expected phase advance in the clock, shown by the T_{min}, and to ensure that the light and melatonin continue to be administered at optimal times to achieve the maximal phase advance. On the first night after the flight the T_{min} would already be advanced to within the sleep period. The flight, as is the case with most flights to Europe from the US, departs in the afternoon and arrives in the morning. As the clock would already be phase advanced all the light exposure upon arrival will occur after the T_{min}, thus producing phase advances and completing re-entrainment. From: Revell VL, Eastman CI. How to trick mother nature into letting you fly around or stay up all night. J Biol Rhythms 2005 Aug;20(4):353–65, by permission.

minimum and in consequence precipitating a shift in the wrong direction. Alternatively dark glasses can be worn during the morning hours in the new time zone. For anyone who suffers greatly from jet lag this approach might well be worthwhile but most people will no doubt find it too burdensome.

In situations where critical performance is required, for example performance in the Beijing Olympics, pre-flight adaptation would be desirable.

Potential new treatments

Endogenous melatonin is thought to facilitate and reinforce sleep and other aspects of night-time physiology, when it is appropriately timed. Exogenous melatonin provides a biological signal for dawn and dusk, to change the timing of the 'internal clock', and promotes sleepiness or sleep during biological day.[86] In most countries its availability is restricted and only recently, for example, has one particular formulation (Circadin) been approved for prescription use in Europe (http://www.emea.europa.eu/humandocs/Humans/EPAR/circadin/circadin.htm). Other formulations are also being developed (e.g., www.alliancepharma.co.uk).

However, melatonin is the precursor of a new class of drugs – chronobiotics. New formulations of melatonin and newly developed analogues have recently become available.[87] Pharmacokinetic properties differ depending on formulation. A recent comparison of fast release, slow release and surge sustained (a combination of fast and slow release components[86]) release preparations suggested that slow release was the most powerful phase shifter in a single dose (M. Paul, personal communication). However, in field studies of jet lag, fast release (5 mg) was more effective than slow release (2 mg) and a lower dose of fast release (0.5 mg).[88] In general lower doses are achieving greater popularity as they have the ability to phase shift in preparation for flight when given during biological day, but the immediate sleep inducing effects are minimised. A combination of pre-flight timed low dose (0.5 mg) and post-flight higher dose with increased sleep induction (3 mg) has been recommended.

The discovery, cloning and characterisation of 2 principle melatonin membrane receptors (Mel1a and Mel1b, now renamed MT1 and MT2), found in numerous locations both in the central nervous system (notably within the SCN) and the periphery, has led to the synthesis of analogues specific for either or both of these receptors.[87] The selective MT1/MT2 receptor agonist known as ramelteon, rozerem or TAK-375 ((*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide), developed by Takeda, has received FDA approval. It is registered for insomnia characterised by difficulty falling asleep, however, it also has chronobiotic properties and a recent report (Zee et al., presented at the Society for research in Biological Rhythms, Sandestin, FA, USA, May 2008) suggests that it can reduce sleep latency after eastward time zone transition.

The compound known as agomelatine, valdoxan or S20098 (*N*-[2-(7-methoxynaphthalen-1yl)ethyl]acetamide), was developed by the Servier Company. It is a potent oral agonist at melatonin MT1 and MT2 receptors and an antagonist at serotonin-2C (5-HT_{2C}) receptors. Its primary development is for depression but it has clear chronobiotic properties and may well be useful in the treatment of jet lag symptoms.

VEC-162 (1R-*trans*)-*N*-[[2-(2,3-dihydro-4-benzofuranyl)cyclopropyl] methyl]propanamide previously known as BMS-214778, is a melatonin receptor agonist with high affinity for both the human MT1 and MT2 receptors ([87]and Vanda Pharmaceuticals Inc., unpublished data). Pre-clinical studies are reported to show that VEC-162 has similar phase-shifting properties to melatonin.

Beta-methyl-6-chloromelatonin (LY156735) is under scrutiny as a potential treatment for insomnia and for jet lag. The first trials reported faster adaptation to a simulated time shift with LY156735.[65]

There are few dose response data for these analogues.

Use and avoidance of short wavelength light

Since light exposure and avoidance of such are the main environmental factors governing adaptation to time zone change, it is of considerable importance that the spectral quality of light strongly influences the circadian response. In the absence of rods and cones, i.e., normal vision, the circadian system can nevertheless respond to light. This observation, made originally in rodless, coneless mice[89] has led to the discovery of a novel circadian photoreception pathway which employs light sensitive retinal ganglion cells with direct neural connections to the SCN, a novel photopigment – melanopsin – and is maximally responsive to short wavelength light (blue, 460–480 nm).[46–48,89] Short wavelength light has greater phase shifting (and melatonin suppression) efficacy in humans than broad spectrum white light with equal numbers of photons.[49,50,90,91] The spectral optimum may depend on the intensity[92] such that in dim conditions green monochromatic light may be more effective than blue: this data has so far been presented not published. However, a comparison of commercially available equipment for inducing phase shifts[93] found that a device delivering monochromatic green light (350 lux) was more effective than a device delivering light with more lux (1500 lux) enriched with blue wavelengths. This observation was confounded by the different sizes of the devices. Nevertheless for scheduled exposure to light pre- and post-flight to hasten adaptation to time zone change it is likely that devices enriched in short wavelengths will be more effective than standard white. There is preliminary evidence that blue enriched light (Philips Lighting) has greater efficacy at maintaining alertness, quality and timing of sleep in an urban office environment[94] and in the Antarctic winter.[95,96] There is also some preliminary evidence that special glasses designed to remove these wavelengths may be useful when light avoidance is recommended but vision must be preserved.[97] However, to date the author is not aware of a commercially available product, or any jet lag studies conducted with these devices.

Predicting tolerance to jet lag (and shift work)

Possibly the most important discovery in recent years regarding the problems of circadian desynchrony relates these problems to a polymorphism in the clock gene *PER3*. In 2000 Archer et al,[35] reported that a variable-number tandem-repeat polymorphism in the coding region of the circadian clock gene *PERIOD3* (PER3, 5/5, 4/5, 5/5) associated with diurnal preference and delayed sleep phase syndrome, with the long variant (5/5) being associated with extreme morningness and the short variant (4/4) with extreme eveningness. Further exploration of this observation included selection of the genotypes 5/5 and 4/4 and subsequent characterisation of the phenotypes. Most importantly the subjects with the 5/5 variant suffered far greater consequences of sleep deprivation in terms of performance (notably during the circadian nadir) than the 4/4 genotypes and these differences could be explained by an effect of the polymorphism on sleep homeostasis – it was associated with greater sleep propensity and a higher proportion of slow wave sleep than the 4/4 genotypes.[32] Related to these observations, Mongrain and Dumont have recently shown that morning types have a higher homeostatic response to sleep disruption than evening types (Fig. 3).[98]

The 5/5 variant is not very prevalent in the UK population (circa 10%). Nevertheless since such subjects will be more susceptible to performance errors in conditions of sleep deprivation such as jet lag and night shift work (there are also preliminary reports of greater susceptibility to breast cancer in women and prostate cancer in men[99,100]) it would be as well for them to be aware of this possibility and take extra precautions. These are the people who should avoid jet lag as far as possible. Extreme morningness is at least

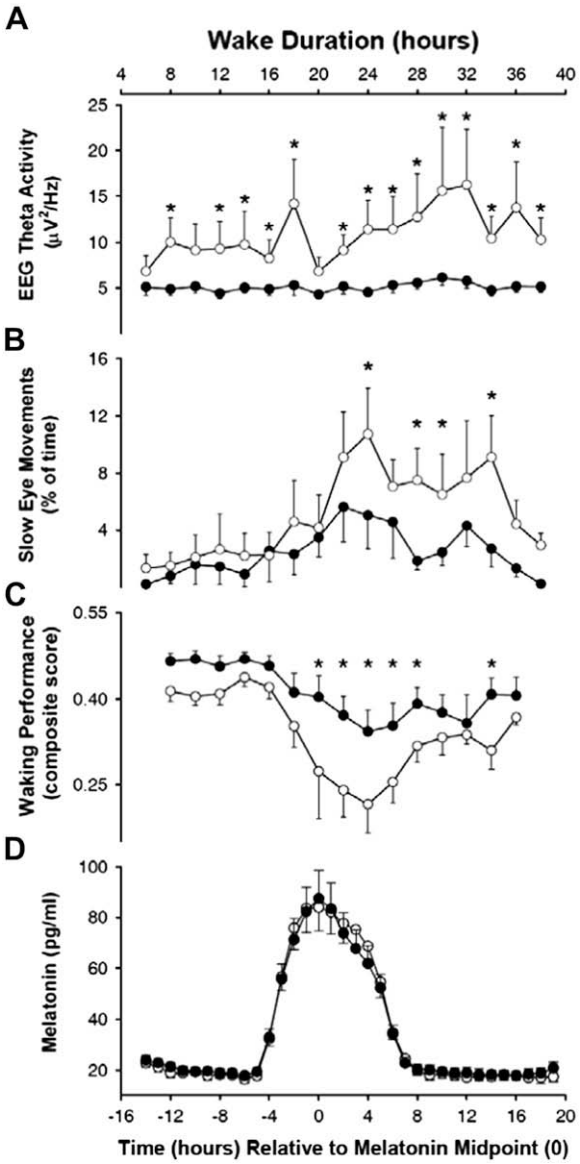

Fig. 3. Deterioration of waking performance and increase of theta EEG activity and slow eye movements during sleep deprivation was greater in PER3 5/5 than PER3 4/4 subjects. Time course of (A) central EEG theta (5–8 Hz) activity during wakefulness, (B) incidence of slow eye movement (SEMs) (percentage of 30 s epochs containing at least one SEM), and (C) waking performance (composite performance score) are plotted relative to the timing of the plasma melatonin rhythm (D) in 10 PER3 5/5 (open symbols) and 14 PER3 4/4 (filled symbols) homozygotes. EEG theta activity, SEMs, and waking performance data were averaged per 2 h intervals, relative to the midpoint of the melatonin rhythm (* indicates a significant difference between genotypes, $p < 0.05$; upper abscissa indicates approximate wake duration). Error bars represent the standard error of the mean. From: Viola AU, Archer SN, James LM, Groeger JA, Lo JC, Skene DJ, et al. PER3 polymorphism predicts sleep structure and waking performance. Curr Biol 2007 Apr 3;17(7):613–8, by permission.

a partial marker for this polymorphism. Moreover morningness has been related to intolerance to shift work in previous studies although not all earlier studies are consistent.[101]

Conclusions

Jet lag is a problem for most time zone travellers, affecting sleep, performance and with possible long-term health consequences. It is due to the misalignment of the internal circadian clock(s) with external time cues. For short stopovers (1–2 days) it is advisable not to try and adapt but to schedule critical activities to daytime in the departure time zone and maintain alertness and sleep by short-term measures such as judicious naps, caffeine and short acting hypnotics. For intermediate length stays (3–5 days) an intermediate phase position between departure and destination time zones with the circadian nadir situated within the sleep period is advisable but difficult to achieve. For long stays in the destination time zone (more than 4–5 days) strategies to hasten adaptation can be employed. These include timed exposure to light of suitable spectral composition and intensity (natural bright light when this can be appropriately timed is best, but will be dependent on season in temperate zones). The American Academy of Sleep Medicine recommends the timed use of the chronobiotic melatonin to hasten adaptation. Melatonin itself is now available in Europe on prescription and melatonin agonists are becoming available. The use of both light and melatonin requires careful attention to timing and, in the case of light, of avoidance as well as exposure. The maximum efficacy for jet lag avoidance is by pre-flight adaptation, however, this requires time and commitment.

Practice points

1. The only guaranteed way of avoiding jet lag is to adapt, or at least partially adapt, to the new time zone pre-flight.
2. For short stopovers there is no point in trying to adapt the circadian system to the new time zone. Current advice is to preserve sleep as far as possible by judicious naps, sleep hygiene measures and possibly short acting hypnotics, and maintain alertness with for example caffeine. Scheduling activities for the period of maximum alertness in the departure time zone is desirable.
3. Correctly timed treatment for jet lag is only possible if a person's circadian phase is known or is predictable. Large individual differences in response to phase shift mean that this is difficult to assess.
4. Assuming a subject is entrained to the departure time zone: for stop-overs of 3–5 days partial adaptation, using the same strategies as for longer stays (see below) by moving the circadian nadir into the sleep period, is desirable.
5. For longer stays and where it is critically important to function well immediately on arrival, pre-flight adaptation is recommended as described in the text. However, timed exposure to bright light in the late evening and avoidance in the early morning of the departure time zone (Westward) or conversely exposure in the early morning/avoidance in the evening of the departure time zone (Eastward) pre-flight and for the first 3–4 days post-flight should initiate a shift in timing of the circadian clock in the right direction. Timed treatment with the chronobiotic melatonin in the early morning of the departure time zone (Westward) or the very early evening of the departure time zone (Eastward) both pre- and post-flight likewise should also initiate and maintain the desirable phase shift. Note that these timings are related to the departure time zone: the last known or predictable internal clock time, both pre- and post-flight. These treatments (light and melatonin) can be combined. More complicated instructions can be given changing the timing of light and/or melatonin daily as the internal clocks (theoretically) adjust. A dose of 0.5 mg melatonin pre-flight and 3–5 mg post-flight is probably optimal.
6. Extreme morning diurnal preference may be associated with greater problems and such people are advised to use appropriate strategies to avoid sleep deprivation.

Research agenda

1. Develop a method for rapid assessment of circadian phase.
2. Investigate the efficacy of short wavelength enriched light for hastening circadian adaptation to the new time zone.
3. Investigate the efficacy of melatonin analogues in the treatment of jet lag symptoms.
4. Investigate any relationships between diurnal preference, genotype and rate and direction of adaptation to different phase shifts/time zone changes.

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