Jet-lag and shift work: (1) circadian rhythms

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Today it is commonplace for people to fly across several time zones on business or on holiday. Moreover, many people work at night rather than the conventional 9-to-5, not only to provide public services but also to use expensive equipment economically and engage in world-wide commerce. Both groups can experience ill-effects, known respectively as 'jet-lag' and 'shiftworker's malaise'[1–4]. In the short term, they feel tired and unable to concentrate, yet cannot sleep uninterruptedly during the night; they perform physical and mental tasks less well than usual and with more errors; they have no appetite and they experience indigestion or bowel upsets. As well as being troublesome at a personal level, these effects might have wider implications—for example, by hampering international negotiations or reducing dexterity in a technical procedure. In the longer term also there are negative effects. For example, there is evidence for raised frequencies of menstrual disorders in airline hostesses[5] and of gastrointestinal ulcers[3] and cardiovascular morbidity in nightworkers[6].

A full explanation of these effects will doubtless indicate that the causes are complex and multiple, but a key issue is the 'body clock'. Here I outline its function and some of the non-pharmacological ways it can be influenced to alleviate jet-lag or shiftworker's malaise. The accompanying article by Arendt[7] focuses on pharmacotherapy.

THE BODY CLOCK

The control of physiological and biochemical variables by negative feedback loops (homoeostasis) is a fundamental property of living organisms. Even so, repeated measurements of variables over a 24-hour period in subjects living conventionally show that daily rhythms exist. Variables associated with activity and food intake, such as core temperature, blood pressure, plasma adrenaline and urinary excretion, are higher in the daytime than at night, whereas those associated with recuperation (plasma growth hormone and cortisol, for example) are higher at night[8]. Such phase differences reflect our lifestyle and environment, but are not completely due to these factors. Thus, if an individual stays awake and sedentary for at least 24 hours, in an environment of constant temperature, humidity and lighting, with identical regularly spaced meals and with uniform mental activity, the rhythms decrease in amplitude but do not disappear[9,10]. There is thus an exogenous component, influenced by lifestyle and environment, and a clock-driven or endogenous component. In subjects living conventionally, these two components are normally in phase.

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In mammals the body clock consists of a pair of nuclei, the suprachiasmatic nuclei, situated in the base of the hypothalamus[11], which rhythmically influence hormones, core temperature and the autonomic nervous system[12]. The body clock is adjusted daily, to run in phase with solar time, by a process termed 'entrainment'; and the means for achieving this are *Zeitgebers*, from the German for time-giver[8,13]. The most important *Zeitgeber* in humans is the light–dark cycle[14–16]. Originally only natural lighting was thought bright enough to serve this function, but the much dimmer light in workplaces and homes has proved strong enough[17]. Other *Zeitgebers* in mammals include cycles of physical activity–inactivity and feeding–fasting; they do not seem to have a large role in human beings, but it would be premature to dismiss them completely at this stage.

How does the timing of the light–dark cycle adjust the body clock? In man, a light pulse in the period up to about 6 hours after the temperature minimum (normally around 0400–0500 h) causes a phase advance; a pulse in the 6-hour period before the minimum causes a delay, and at other times does not shift the body clock. The information is believed to reach the suprachiasmatic nuclei by a direct pathway from retina to hypothalamus. There may also be a pathway from skin, since a phasic shift can be induced by shining bright light on the back of the knees[18].

The body clock is influenced also by melatonin signals from the pineal gland, receptors for this hormone being present in the suprachiasmatic nuclei[19]. Melatonin exerts its phase-shifting effects in the opposite direction to those of light, delaying the clock when administered just after the temperature minimum and advancing it when given in the hours before it[20].

The effect of the body clock is to separate the functions of the body into those associated with active and recuperative phases—normally in the daytime and at night, respectively[21].

RESPONDING TO CHANGES IN TIMING OF THE SLEEP-WAKE CYCLE

The clock is slow to adjust its phase to a change in the timing of an individual's habits and environment. Normally this is advantageous, a brief daytime nap or transient nocturnal awakening not producing a change in the timing of the body clock; but when the change of habits is more permanent there will be a mismatch between the endogenous and exogenous components of the rhythms. It is this lack of synchrony between the body clock and the environment, together with the abnormal phasing between different rhythms, that is believed to account for the symptoms of jet-lag and shiftworker's malaise.

DEALING WITH JET-LAG

There are numerous strategies for reducing the ill-effects of long-haul flights—for example, the timing of eating and napping, guarding against cramp and dehydration, and the careful use of hypnotics. Here I concentrate on attempts to adjust the body clock to the new time zone. Note, however, that adjustment will take up to five days after an eastward transition of ten time zones, slightly less after a similar transition to the west[1,4]; thus, for stays of only a few days the traveller is recommended to time appointments in the new zone to coincide with daytime at home.

Mealtimes

The timing and composition of meals has been proposed as a *Zeitgeber* in man[22]. The rationale is that a high-protein breakfast will raise plasma tyrosine, and that this will promote the transfer of tyrosine rather than tryptophan across the blood–brain barrier. By contrast, a high-carbohydrate evening meal will raise plasma tryptophan, promoting preferential uptake of tryptophan. The next stage, which does not have unambiguous experimental support[23], is that enhanced uptake of tyrosine will increase the synthesis and release of adrenaline, noradrenaline and dopamine, causing a general activation of the body; also, enhanced uptake of tryptophan will cause synthesis and release of serotonin and melatonin, so promoting sleep. Testing of the 'feeding hypothesis' has encountered methodological difficulties; the effects, if any, were only slight.

Physical activity

In hamsters[24], provision of a new running wheel, certain drugs and the presence of a potential mate all caused an extensive bout of physical exercise that could promote adjustment of the body clock. In man, the results of a bout of exercise have been less convincing: small delays of several rhythms have been produced[25], but advances of the body clock, as would be required by eastward travellers, have been more difficult to achieve. The cause of the apparent species difference is not known but the amount of exercise may be relevant: a new wheel can induce the hamster to run more than 5 km in 3 hours, and the equivalent exercise for a human might be more than the average traveller was prepared to take.

Bright light

Most of the data on bright light in man come from laboratory-based experiments[14–17] and few from field studies. In principle, however, after an eastward flight of up to nine time zones the aim must be to promote an advance of the body clock by exposure to light in the hours after the core temperature minimum (0500–1100 h), and avoidance of light in the hours before the minimum, when a phase delay would be produced (2100–0300 h). For flights through more than nine time zones to the east, and for all westward flights, the aim is rather to promote a delay of the clock by exposure to light in the 6 hours before the temperature minimum and avoidance of light in the 6 hours after it.

Tables have been published that translate this protocol into periods of exposure to light and avoidance of it in terms of local times in the new time zone[2,4]. Living in accord with the habits of the inhabitants in the new time zone ('when in Rome, do as the Romans do') produces the right times of exposure to light after a flight to the west, but such a behaviour pattern is often inappropriate after time-zone transitions to the east. For example, after a flight from the UK to Los Angeles (eight time zones to the west), light is required at 1300–1900 h local time (equivalent to 2100–0300 h on 'body time'), and should be avoided between 2100 and 0300 h local time (0500–1100 h on body time). This requirement fits in easily with the natural lighting in Los Angeles. By contrast, after a flight from the UK to Hong Kong (eight time zones to the east), light is required at 1300–1900 h on local time (equivalent to 0500–1100 h on body time), and should be avoided between 0500 and 1100 h local time (equivalent to 2100–0300 h on body time). Unfortunately, the traveller to the east who tries to promote adjustment by 'getting out and about' at the first opportunity might actually be delaying the body clock—probably one reason why jet-lag tends to last longer after an eastward flight than after a westward flight.

Portable light sources, in the form of battery-operated visors, allow a traveller to switch on as necessary, even during the flight; few detailed reports of their efficacy have been published. Since, when the above light protocol is used, it is also important to avoid light at other times, the traveller should wear strong sunglasses or, preferably, stay indoors at certain times.

DEALING WITH NIGHTWORK

Like travel across time zones, nightwork requires individuals to sleep and work at times that clash with the phase of their body clock, and adjustment of the clock should be advantageous. However, the difficulties associated with nightwork are more complex. First, during nightwork the individual's lifestyle is different from that of the partner, the family and many colleagues. A complete adjustment to nightwork would accentuate disparity. Second, facilities for the nightworker, such as restaurants with wholesome and appetizing food, and things to do during the 'lunch break' (around 0100 h) are often poorer than those for the day worker—or even absent. Third, sleep at home in the daytime requires special consideration from the household and friends; even if this is forthcoming, there will be difficulties if the house is in a busy area with noise from traffic audible in the bedroom. Fourth, nightworkers commonly go to bed immediately after the night shift, so that work comes at the end of the waking period; in day workers, work comes at the beginning of the wake period when the individual is less fatigued. Fifth, nightwork generally applies to individuals for a substantial fraction of their working time, often extending over years; a comparable frequency of changes of the sleep–wake pattern rarely applies to any but air crew regularly engaged in long-haul flights or the most ardent jet-setter.

Thus, much advice can be given to the nightworker, the household, and those who devise shift schedules. But even then, there is still the problem of promoting adjustment of the body clock to the changed sleep–wake cycle.

PROMOTING ADJUSTMENT OF THE BODY CLOCK

As with time-zone transitions, adjustment cannot be accomplished if there is a rapid rotation of shifts. With a slower rotation of shifts—at least five consecutive nights, for example—adjustment is possible; but, even with 'permanent' nightworkers, it must be remembered that reversion to a conventional sleep–wake schedule during rest days will quickly undo the body clock's adjustment to nightwork.

The accompanying article[7] discusses the use of melatonin. What of non-pharmacological strategies?

Mealtimes

The role of mealtimes in promoting adjustment of the body clock in nightworkers does not seem to have been investigated. However, the social function of communal mealtimes, both at work and at home, might act to reinforce the idea of a changed sleep–wake schedule or to maintain family contacts.

Exercise

Neither has the use of timed periods of exercise been tested. Nevertheless, some research indicates that shift workers benefited from a general exercise programme[26]; whether this benefit was due to an increase of fitness rather than to phase shifting of the body clock is not known.

Bright light

Several reports exist, generally concerning volunteers in laboratory-based simulations of nightwork, of attempts to promote adjustment of the body clock by exposure to bright light[27,28]. Use of bright light during the first part of the night shift delayed the core temperature change to match the delay of sleep times. These results indicate that adjustment of the body clock can be produced more completely and rapidly by this method.

Two field studies upon nurses working night shifts have been published. The first used light boxes in a room near the ward that was occupied by the nurses at the start and end of the night shift as well as during rest breaks[29]. The second used light visors worn throughout the shift[30]. The phase-shifting effects were small, but the reason may be that the light was available throughout the shift (so combining possible phase-advancing and phase-delaying effects) and was used for only two nights (for such a rapidly rotating shift system, adjustment of the body clock would have been neither possible nor desirable). Nevertheless, there was a positive effect upon mood, and this might turn out to be of benefit to all nightworkers[31], irrespective of the speed of rotation of their shift system.

As with the use of light after time-zone transitions, if a phase delay of the rhythms is required then care must be taken not to expose the worker to too much light after the minimum of the core temperature rhythm, and so cause a phase advance. To prevent any unwanted advance, the light can be dimmed towards the end of the first night shift and, if the subject returns home in daylight, he or she should wear dark goggles.

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