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Review Article

The use of melatonin in jet lag

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Circadian rhythm or body time is the major biological endogenous rhythm (sleep, body temperature, cortisol production) and is generated and coordinated by a circadian master oscillator located in the anterior hypothalamus area, the suprachiasmatic nuclei (SCN) (1). Human circadian rhythms have a free-running period of approximately 24.5 hours (range 22.5–27.5 hours (2), however, normally the rhythm is entrained to the exact phase length of the external day-night cycle by environmental time cues (or 'zeitgebers').

Melatonin (N-acetyl-methoxytryptamine), a methoxyindole, is the primary hormone secreted by the pineal gland. The pineal gland occupies the depression between the super colliculi of the mesencephalon, and has a mass of 50 – 150 mg (3). Melatonin is synthesised from the amino acid tryptophan, via the intermediate serotonin.

Activity of the enzymes involved in this synthesis is high during the dark phase of the day. As such, melatonin production occurs almost exclusively at night under normal conditions. Transmission of information occurs from the retina to the SCN and then to the reticular system, spinal cord and cervical ganglia. From there, post-ganglionic sympathetic fibres reach the pineal gland. The number of β-receptors rises during the latter part of the light phase, noradrenergic stimulation begins in the dark phase and down regulation of β receptors occurs through the course of the night (3). The secretion of melatonin itself starts as soon as darkness falls and usually peaks between about 02:00 and 04:00 hours. Since the duration of melatonin secretion depends on the duration of darkness, a greater amount of melatonin in secreted over 24 hours in Winter than in Summer.

Melatonin is rapidly metabolised by the liver; more than 85% is excreted as 6-sulphatoxymelatonin (6-SMT) (4). The rhythm characteristics of melatonin and 6-SMT are highly reproducible in the same individual. Melatonin concentrations in humans begin to increase from the age of three months and concentration peaks between one and three years of age. Young adults secrete 5–25 μg of melatonin per day and this amount decreases markedly with age (5). Jet lag, or circadian dyschronism occurs after rapid long haul flights across several time zones and is characterized by various symptoms; fatigue (with inability to sleep at the new night time), headache, irritability, loss of concentration and gastrointestinal disorders such as indigestion, loss of appetite and bowel irregularities (6). As yet, the symptoms of jet lag are not standardised, making comparisons between studies difficult. A more systematic scale, (the Columbia Jet Lag Scale) adopted by Spitzer et al. (7) identifies a high consistency of the items fatigue, difficulty in concentrating, clumsiness, decreased alertness in the daytime, difficulty with memory, general weakness, dizziness, lethargy and daytime sleepiness–symptoms which may be experienced to differing extents, or not at all, within a group of individuals.

Flight across more than three time zones causes a problem because the environmental (local time in the new time zone) and internal (body time or circadian rhythm) become desynchronised. Symptoms of jet

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lag increase with the number of time zones crossed, with eastward flights usually resulting in slower adaptation than westward flights. The severity of the symptoms may also be related to the phase of the menstrual cycle. It should be noted that the symptoms do not occur after long distance flights to the south or the north, since local time does not change, and that symptoms can be generated in the laboratory, where the only change is to local time (6). The temperature rhythm of a normal person before and immediately after flights through eight time zones differs markedly. For a person who usually sleeps between 2400 and 0800h and is mainly sedentary during the day, the urge to sleep occurs when the core body temperature is low, i.e. between 2400 and 0800h in London, between 0800h and 1600h in Hong Kong (8h eastward shift), and between 1600h and 2400h in Los Angeles (8h westward shift). Therefore the individual will have difficulty getting to sleep at the new night time and will feel tired in the morning in Hong Kong, and in Los Angeles will have difficulty remaining asleep in the morning but feel tired in the afternoon and the evening, due to inappropriate phasing of the circadian rhythm.

Hormonal changes associated with jet leg have been studied. Five subjects flew westward through seven time zones from Brussels to Chicago and then after 30 days eastwards back to Brussels by the same route (8, 9). Total plasma protein (TPP) daily variation was found to be posture dependant, with transient disruptions of the 24 hour TPP pattern observed in a significant number of subjects one day after the flights, and was more severe after the eastward flight. The time shifts did not induce quantitative alterations in adrenal secretion, however the acrophase (time of maximum secretion) and quiescent period of the 24 hour pattern of ACTH and cortisol were disrupted. Differences in the adaptation of these two hormones suggested that the various components of the pituitary-adrenal periodicity may be under different controls. Adaptation of the acrophase to the new clock time was complete on the eleventh day after both westward and eastward shifts, though the quiescent period needed longer to adapt, especially after the westward flight. There was no consistent correlation found between subjective discomfort and ACTH-cortisol periodicity. Total desynchronisation of the melatonin profile was observed after the eastward flight, which involved 33 hours of sleep deprivation. Also, greater perturbations of sleep and subjective discomfort occurred after this flight. The melatonin acrophases were fully adapted to local time eleven days after travel in both directions. As yet, it is not known if such disruption of the melatonin acrophase plays a part in the psychological disturbance of jet lag.

As described, one of the main problems with jet lag is sleep loss. After flying eastward, the individual tends to find difficulty in getting to sleep at the new bedtime, whereas after flying westward the problem tends to be premature awakening. Jet lag therefore can affect individuals in a variety of ways, for example, holiday makers may enjoy their holiday less and business men may be prone to errors. Samel et al. (10) suggested there is a causal link between errors and accidents and jet lag in pilots on long haul flights to the east and the west. Pilot fatigue, which could be associated with worsened performance, increased during flights – particularly night flights to the east. Additionally, electroen-cephalographic (EEG) recordings indicated a mean occurrence of up to five ‘microevents’ or ‘microsleeps’ (that is ‘an eight second period with α activity is above a certain threshold’ (6) per hour during the cruise phase of the flight. Jet lag may also have adverse effects on competing athletes since circadian rhythm is directly relevant to athletes. Most athletes perform at their personal best at about 18:00 hours, when muscle strength, adrenaline secretion, short term maximal power output, self chosen

work rate, speed of mental performance (reaction time and manual dexterity) are at their greatest and the perceived exertion for a given amount of exercise is at its least (11). Therefore, a loss of sleep coupled with attempting exercise at a time perceived as night by the body clock, results in poorer training and competition results in athletes travelling to other time zones.

Reppert et al. found melatonin receptors in the SCN (12) and they are believed to be the means by which melatonin acts as an internal time cue. The retinohypothalamic tract is a direct pathway between the retina and the SCN and is thought to act via the excitatory amino acid glutamate and induction of immediate early genes (6). Additionally, in hamsters the pathway (to the SCN) for non-photic zeitgeber activity is thought to be via the intergeniculate leaflet, and it is possible (though not established) that it is via this pathway that mental, physical and social rhythms combine to act as a zeitgeber in humans.

Jet lag trials

If a method of treating or preventing jet lag is to be valuable it should be efficacious, readily available, convenient to use and have no major side effects. Several trials have been carried out regarding the use of melatonin in jet lag. Arendt et al. recognised that ‘a means of rapidly resynchronising body rhythms to local time would be of benefit to individuals who suffer markedly from jet lag’ (13). In a double blind study (13), 17 healthy adult volunteers flew from London to San Fransisco (8 time zones west) where they remained for 14 days in order to adapt to local time. The volunteers took 5 mg melatonin or placebo at 1800 hours local time for three days prior to the return flight, and on their return to London took the same preparation at 2200-2400 hours local time for a further four days. The subjects rated their jet lag on a visual analogue scale (VAS) on day seven after arrival home. Here, patients were asked to rate their jet lag on a scale of 0 to 100 (ranging from insignificant to very bad). Jet lag was deliberately not defined since it is a highly variable condition with symptoms that vary from person to person. None of the subjects who took melatonin rated their jet lag as significant whereas six out of the nine subjects who took placebo did. Biochemical data showed that endogenous melatonin and cortisol resynchronised more rapidly in subjects taking melatonin than placebo. The study therefore indicated that melatonin did alleviate jet lag, however the study was very limited. Ideally, studies needed to be extended to larger numbers of subjects, include westward as well as eastward flight, different numbers of time zones crossed, and at different times of the year.

In a double-blind study conducted by Petrie et al. (14) twenty adult volunteers flew from Auckland to London (12 time zones east), returning on a similar westward flight three weeks later. Subjects received either placebo or 5 mg melatonin for three days before the outward flight at 1000-1200 hours (local time) and for three days after arrival at 2200-2400 hours (local time) and the placebo on the return flight. Subjects rated their feelings of jet lag and tiredness on a VAS before the departure of both flights, on arrival and several times after arrival. Additionally subjects filled in questionnaires relevant to jet lag, recording their hours of sleep and undertook retrospective rating of jet lag, and were asked whether they thought they had taken melatonin or placebo. The melatonin group reported less jet lag, faster establishment of normal sleep pattern, a quicker return to normal energy levels, and less daytime tiredness than the placebo group. All subjects suffered more severe jet lag on the return (westward) than the outward (eastern) flight. Therefore, the results of this study also support the use of melatonin for alleviating jet lag and tiredness after long haul flights. The 5 mg dose of melatonin was also well tolerated, with few side effects reported– two subjects reported a mild sedative

effect, and one subject reported feeling more relaxed. Again, however, an optimum dose or dosing schedule was not determined and the group size was small. The symptoms of jet lag were not standardised in either study, making comparisons difficult. No baseline measures to control for symptoms unrelated to jet lag were taken, for example previous fatigue, stress due to travel and inability to sleep in a novel environment (7).

Other studies were carried out over the next ten years. In a trial conducted by Nickelsen et al. (15), healthy adult volunteers were flown both westerly and easterly over six to seven time zones (12 subjects), eight to nine time zones (12 subjects) or ten to eleven time zones (12 subjects). After the westbound flight, volunteers were given melatonin or placebo at bedtime for seven days, stayed for fourteen days or more at the destination and on their return, took melatonin or placebo for five days. A constantly accelerated acrophase shift of salivary cortisol occurred indicating effects on the circadian rhythm, and was more significant in those crossing eight or more time zones. A double blind trial investigating the optimal time for taking melatonin in a group of 52 international cabin crew was carried out by Petrie et al. (16). The subjects were assigned to three groups; early melatonin (5 mg started three days prior to arrival until five days after return home); late melatonin (placebo for three days then 5 mg melatonin for five days); and placebo. Compared to placebo, the late melatonin group showed an improvement in jet lag, mood and sleepiness while the early melatonin group had a worse recovery. Retrospective rating also indicated significantly less jet lag and sleep disturbance following the flight, and a faster recovery of energy and alertness in the late melatonin group compared to both placebo and the early melatonin group. In fact, the melatonin group demonstrated a worse overall recovery than placebo. The results of this study suggest that melatonin has a detrimental effect on circadian rhythmicity if the subject is not adapted to a time zone. 586 travellers were analysed in one large sample pooled across many studies (474 subjects taking melatonin, 112 subjects taking placebo) (17). Arendt and Deacon found a 50% reduction in self rated jet lag in the melatonin group using VAS (17). They concluded that, if ingestion of melatonin is correctly timed, its use may alleviate some of the symptoms of jet lag by enhancing sleep and alertness, and hastening resynchronisation of body rhythms to the new local time. However, they felt that research was still needed to determine dose optimisation and formulation and fully evaluate the effects of melatonin on sleep architecture and performance. The only detected side effect of melatonin in this study was sleepiness (present in 8.3% of the melatonin group and 1.8% of the placebo group). The effect of 3 mg melatonin on jet lag after an 8 hour eastward flight was studied (18). Six male adults were flown from Tokyo to Los Angeles. Upon arrival, they were exposed to natural daylight outdoors from the late morning and took 3 mg melatonin at 2300 hours. Melatonin was found to accelerate the rate of resynchronising the circadian melatonin rhythm and was thought to be useful in jet travel from Tokyo to Los Angeles.

Jet lag simulation studies have also been used in which easterly travel was simulated by advancing the sleep wake cycle by 9 hours. In the first cross over, double-blind study with eight healthy male adult subjects (19) some physiological rhythms (temperature, urinary excretion of corticosteroids, 6-SMT, sodium and potassium) resynchronised faster in the melatonin group. However there were no significant differences in daytime fatigue, tenseness, sleepiness, or psychomotor performance and only a minor advantage in subjective alertness. This, suggests that treatment can be useful in resynchronising the melatonin rhythm after eastward time zone transitions, though evidence is not sufficiently great to

recommend melatonin for the alleviation of jet lag. In the second study of 7 healthy young adult subjects (20, 21), melatonin ingestion showed an immediate benefit on alertness and performance even before circadian shifts occurred. This indicated that improvement of the symptoms of jet lag might occur independently of body rhythm resynchronisation and it was concluded that the laboratory model was a useful and inexpensive method for studying adaptation strategies in real life.

Spitzer et al. used a revised version of their Columbia Jet Lag Scale (7) which identifies prominent daytime symptoms in a randomised, double-blind trial of placebo and three alternative regimens of melatonin (5 mg at bedtime, 0.5 mg at bedtime and 0.5 mg taken on a shifting schedule). 257 subjects took part in the trial, having stopped over in New York for four days. There were marked score increases in all four groups on the first day home, with progressive improvement over the next five days, however none of the melatonin regimens showed significant improvement over placebo. The results of this study were surprising as they contrast with the positive findings of other research. This was a strong study in the respect that the group size was large and the daytime symptoms of jet lag were more objective due to the use of the jet lag scale. The study however did have several limitations. Some symptoms which might be more closely related to circadian rhythm disturbance were not studied, for example difficulty with falling asleep, remaining asleep and early morning wakening. The four day stopover in New York may not have been adequate for many subjects to syncronise their body rhythms to the new local time. It was recognised that the time of administration of melatonin had not been optimised, as was the case with most studies. It is also possible that there was a large placebo effect, resulting from the three-quarter chance of receiving melatonin and that subjects in other studies had responded positively to melatonin because they had detected its presence.

Jet lag may induce or exacerbate mental disorders. Tourists arriving in Israel after an eastbound flight who were found to have aggravated psychotic symptoms were observed at the Jerusalem Mental Health Centre (22). It is thought that psychosis is worsened by jet lag because of the way in which jet lag manifests; severe night time insomnia, daytime tiredness, agitation and disorganised behaviour. Other factors such as religion, language problems, lack of family and community support and a lack of familiarity with the local health care system may further compound the problem. Such individuals may be treated with strong antipsychotics in the destination country when it is possible that exogenous melatonin can alleviate psychotic exacerbation linked to jet lag. Seven patients admitted to the acute ward were treated with 6 mg melatonin at night. Sleep patterns were restored in all seven patients quickly. Four patients received melatonin concomitantly with their antipsychotic medicines–resolution of psychotic symptoms occurred within three to fourteen days. Three patients were treated with melatonin alone, antipsychotics were reserved in case of need, but were not found to be necessary. No side effects were attributed to the use of melatonin. Treatment with melatonin alone was found to be a useful and safe first line treatment for psychotic exacerbations linked to jet lag, with use of antipsychotics as second line treatment.

The mechanism of melatonin action is not known for certain. As described, melatonin can advance or delay the body clock according to when it is ingested. However it may also have a hypnotic action due to its temperature lowering abilities that may be attributed to its actions on peripheral blood vessels (23, 24), i.e. melatonin acts separately as a chronobiotic and hypnotic. If melatonin is to be used for its temperature lowering, hypnotic effect it should be taken at approximately 2000

hours at the new local time, irrespective of the flight that had been undertaken. However, if melatonin is to be used as a chronobiotic it should be taken at a certain time (according to the direction of travel and number of time zones crossed) to phase advance or phase delay endogenous rhythms. The usefulness of melatonin in jet lag could be due to either its chronobiotic effects, its hypnotic effects or both.

A recent Cochrane review (25) assessed nine trials comparing melatonin with placebo, and one trial comparing melatonin with zolpidem, a drug used short term for insomnia. In nine out of the ten trials, taking melatonin at the desired bedtime at the destination (2200–2400 hours) decreased jet lag resulting from crossing five or more time zones. 5 mg, 0.5 mg and 2 mg sustained release (SR) doses were compared: 5 mg and 0.5 mg doses had a comparable effect, but 5 mg dosing resulted in faster onset and better quality of sleep. The 2 mg SR dose was found to be less effective than non-SR formulations that give higher and more short-lived peaks of drug concentration in the body. It was also concluded that taking melatonin at the wrong time of day could in fact cause a delay in adaptation to local time, therefore the timing of doses is very important. The safety profile of melatonin was shown to be high in these trials; therefore melatonin could be safely recommend for adults crossing five or more time zones, especially if the individual had suffered jet lag before.

Adverse effects

Adverse effects of melatonin ingestion may occur due to its hypnotic effects. It has been suggested that taking melatonin can have negative effects on mental performance and alertness, possibly as a residual effect of a poorer quality of sleep, though studies on this issue have been contradictory (26, 27). Zhdanova et al. (28) suggested that allowing subjects to sleep after melatonin ingestion removed residual effects on mood and mental performance, and Arendt combined results of her trials to find that daytime sleepiness occurs in approximately 8% of subjects after ingestion of a 5 mg dose (5). One study comparing different doses for men and women, suggested the use of personalised medication levels to avoid side effects (29). While short term studies indicate melatonin has a very low toxicity, no long-term safety data exists. In all the studies reported here, subjects were healthy adults given medication on a named patient basis on prescription. There is no data available on uncontrolled preparations that are available for purchase over the counter in the United States, for example. Melatonin is known to cross the placenta, and receptors for the hormone are present in the foetus, with high placenta melatonin levels leading to abnormalities of the unborn child (4), therefore it should not be recommended in pregnancy or breast-feeding. Neither beneficial effects nor safety have been investigated in children, so use should be avoided in this patient group. There is not extensive knowledge of the interactions of melatonin with other medications, though its use should be avoided in patients taking monoamine oxidase inhibitors. Use of melatonin should also be avoided in patients with allergies or autoimmune disease and those with severe mental illness (4). Such information demonstrates why countries may have different regulations over the availability of melatonin. In Britain, the Medicines Control Agency (MCA) has restricted it to prescription on a named-patient basis only, and promotion of melatonin is unlawful due to a lack of British licensed products. In the United States melatonin is available over the counter as a food supplement, and it is legal for a British resident to bring melatonin purchased in the US home for personal use.

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