

A multifactorial approach employing melatonin to accelerate resynchronization of sleep–wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes

Cardinali DP, Bortman GP, Liotta G, Lloret SP, Albornoz LE, Cutrera RA, Batista J, Gallo PO. A multifactorial approach employing melatonin to accelerate resynchronization of sleep–wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes. *J. Pineal Res.* 2002; 32: 41–46. © Munksgaard, 2002

Abstract: Rapid transmeridian translocation through multiple time zones has a negative impact on athletic performance. The aim of the present study was to test the timely use of three factors (melatonin treatment, exposure to light, physical exercise) to hasten the resynchronization of a group of elite sports competitors and their coaches to a westerly transmeridian flight comprising of 12 time-zones. Twenty-two male subjects were included in the study. They were professional soccer players and their coaches who travelled to Tokyo to play the final game of the Intercontinental Coup. The day prior to departure, urine was collected from each subject from 18:00 to 06:00 hrs to measure the melatonin metabolite 6-sulphatoxymelatonin. Participants were asked to complete sleep log diaries from day 0 (preflight) to the day before returning to Buenos Aires (day 8). All subjects received 3 mg of melatonin p.o. daily at expected bedtime at Tokyo immediately after leaving Buenos Aires. Upon arrival at Tokyo the subjects performed a daily physical exercise routine outdoors at two restricted times of the day (from 08:00 to 11:00 hrs in the morning and from 13:00 to 16:00 hrs in the afternoon). Exposure to sunlight or physical exercise at other times of the day was avoided. Except for the number of awakenings (which increased on days 1 and 3) and sleep latency (which decreased on days 2, 6 and 8), there was an absence of significant changes in subjective sleep parameters as compared with preflight assessment. Sleep quality and morning alertness at Tokyo correlated significantly with preflight 6-sulphatoxymelatonin excretion. Mean resynchronization rate of sleep–wake cycle to the 12 hr-time shift was 2.13 ± 0.88 days, significantly different from the minimal resynchronization rate of 6 days expected after a 12-time-zones flight. The results indicate that the combination of melatonin treatment, an appropriate environmental light schedule and timely applied physical exercise can be useful to help elite athletes to overcome the consequences of jet lag.

Daniel P. Cardinali¹, Guillermo P. Bortman², Gustavo Liotta², Santiago Pérez Lloret¹, Liliana E. Albornoz¹, Rodolfo A. Cutrera¹, Jorge Batista² and Pablo Ortega Gallo²

¹Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina; ²Departamento Médico, Club Atlético Boca Juniors, Buenos Aires, Argentina

Key words: athletic performance, jet lag, light exposure, melatonin, physical exercise, sleep–wake cycle, 6-sulphatoxymelatonin

Address reprint requests to Daniel P. Cardinali, Departamento de Fisiología, Facultad de Medicina, UBA, Paraguay 2155, 7o. Piso, 1121 Buenos Aires, Argentina.
E-mail: cardinal@mail.retina.ar

Received April 13, 2001;
accepted June 14, 2001.

Introduction

Athletes often travel across multiple time zones in order to engage in national or international competitions. Although rapid transmeridian translocation, which produces a sudden disorder between the 'Zeitgebers' of the new geographical place and the traveller's circadian system, i.e. 'jet lag' (Waterhouse et al., 1997), has a negative impact on athletic performance (Winget et al., 1985; Loat and Rhodes, 1989; O'Connor and Morgan, 1990; Hill et al., 1993; Jehue et al., 1993; Recht et al., 1995; Manfredini et al., 1998; Youngstedt and O'Connor, 1999), travel

across multiple time zones has become a common feature in the lifestyle of contemporary international sports competitors.

Any traveller needs some days to adapt himself/herself to the new situation, unless he/she stays in an environment that is totally isolated from outside and with lights on and off in the way of his usual residence. The time taken to adapt depends on the size of the phase-shift and Zeitgeber strength (for example, photoperiod and light intensity), but often approximates to 1–1.5 hr of adaptive shift per day, with worsening of symptoms after an eastbound flight as compared with a westbound flight (Deacon and Arendt,

1996; Waterhouse et al., 1997; Arendt, 1998; Czeisler and Brown, 1999; Gherardin, 1999). Because daily rhythmical oscillations occur in several physiological and behavioural functions that contribute to athletic performance (e.g. sensory motor, perceptual and cognitive performance; neuromuscular, behavioural, cardiovascular, and metabolic variables), these rhythms can significantly influence performance depending upon the time of day at which the athletic endeavour takes place.

However, scant information is available on the possible procedures to accelerate resynchronization rate after a transmeridian flight and hence to improve the actual performance of elite sports competitors. The aim of the present study was to test several possible countermeasures to jet lag given simultaneously. They include the timely use of three factors (melatonin treatment, exposure to light, physical exercise) to hasten the resynchronization of a group of professional soccer players and their coaches to a westerly transmeridian flight comprising 12 time-zones.

Methods

Twenty-two male subjects were included in the study. The mean \pm S.D. age was 29.7 ± 8.7 yrs. They were professional soccer players and their coaches from Boca Juniors Club, Buenos Aires, who travelled to Tokyo to play the final game of the Intercontinental Cup against Real Madrid, Spain. The team left Buenos Aires on 11/21/00, and arrived at Tokyo (12 hr time shift) on 11/23/00, via Los Angeles. The game was held on 11/28/00, (day 7) and the team stayed at Tokyo till next day. The day prior to departure, urine was collected from each subject for 12 hr (from 18:00 to 06:00 hrs) to assess the production rate of melatonin by measuring the urinary melatonin metabolite 6-sulphatoxymelatonin.

Lighting conditions of the aircraft and in-flight meal schedule were set at Tokyo time zone from the beginning of the flight (Varig, business class). Time of sunrise and sunset in Buenos Aires and Tokyo on November 23rd were: Buenos Aires: 05:35 hr sunrise and 19:49 hr sunset; Tokyo: 06:29 hr sunrise and 16:30 hr sunset. Therefore, daylength was as an average about 14 hr in Buenos Aires and 10 hr in Tokyo (Fig. 1).

All subjects received gelatin capsules containing 3 mg of melatonin (Melatol^R, Elisium S.A., Buenos Aires, Argentina) p.o. daily 30 min before expected sleeping time at Tokyo immediately after leaving Buenos Aires and for the time of the study. Data on melatonin purity, as provided by the supplier, indicated that it was more than 97% pure by infrared and ultra-violet (UV) spectra and by high pressure liquid chromatography (HPLC); not more than 1.0% total and not more than 0.3% of any individual impurity were found.

Upon arrival at Tokyo the subjects performed daily physical exercise routines outdoors at two restricted times of the day (from 08:00 to 11:00 hrs in the morning and from 13:00 to 16:00 hrs in the afternoon) (Fig. 1). Exposure to outdoor light or physical exercise at other time of the day was avoided. This routine was kept till the game (day 6). The incumbent physicians monitored potential adverse effects throughout the study.

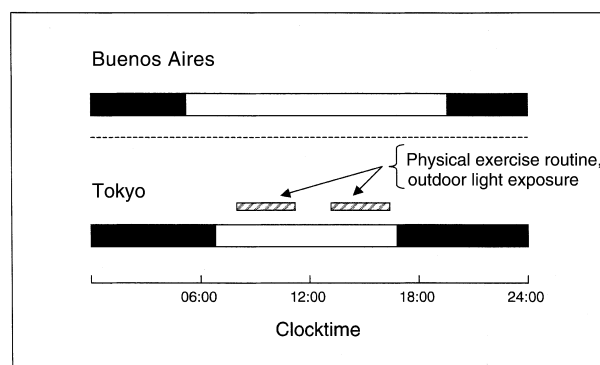


Fig. 1. Diagram showing the lighting exposure and physical exercise routine schedule employed. Upon arrival at Tokyo (on November 23rd) the subjects performed daily physical exercise routines outdoors at two restricted times of the day (from 08:00 to 11:00 hrs in the morning and from 13:00 to 16:00 hrs in the afternoon). On November 23rd the time of sunrise in Buenos Aires and Tokyo was 05:35 and 06:29 hrs, respectively, while the time of sunset was 19:49 and 16:30 hrs, respectively.

Participants were asked to complete sleep log diaries to evaluate overall quality of sleep, time to bed, time wake, number of awakening episodes and general sleep information from day 0 (at Buenos Aires) to day 8 (last day in Tokyo). The subjects were asked to assess every day the quality of their sleep, morning freshness and daily alertness graphically on a 10-cm long line rated from 0 to 10 (visual analogue scale).

Individual actograms were constructed from sleep log diaries (time to bed, time wake) by using the Circadia Data Analysis Program, version 2.1.16, Behavioural Cybernetics. Phase-shifts were determined by eye fitting as described by Daan and Pittendrigh (1976). Briefly, a line was fitted visually along the sleep onsets, minimizing its variability, for the last 4–5 days of the actograms. The number of days taken by every individual to reach that line, starting from the first day of the actogram, was computed.

6-Sulphatoxymelatonin was measured by a specific radioimmunoassay (RIA) (Arendt et al., 1985). All samples were measured in the same assay with an intra-assay coefficient of variation of 6%.

Results were statistically analysed by a Friedman test (nonparametric repeated-measures, ANOVA) and by a paired Wilcoxon's test, or by rank correlation analysis. A Students' one-sampled *t*-test was used for comparison between expected and observed resynchronization rates.

Results

Fig. 1 shows schematically the lighting exposure and physical exercise routine schedule employed in the study. Several self-assessed sleep parameters in soccer players and their coaches undergoing the combined resynchronization routine before, during and after a 12 time-zone transmeridian flight are summarized in Fig. 2. Total sleep duration, sleep latency, sleep quality, number of sleep awakenings and morning alertness obtained for nine subsequent days are depicted. The first day was the day

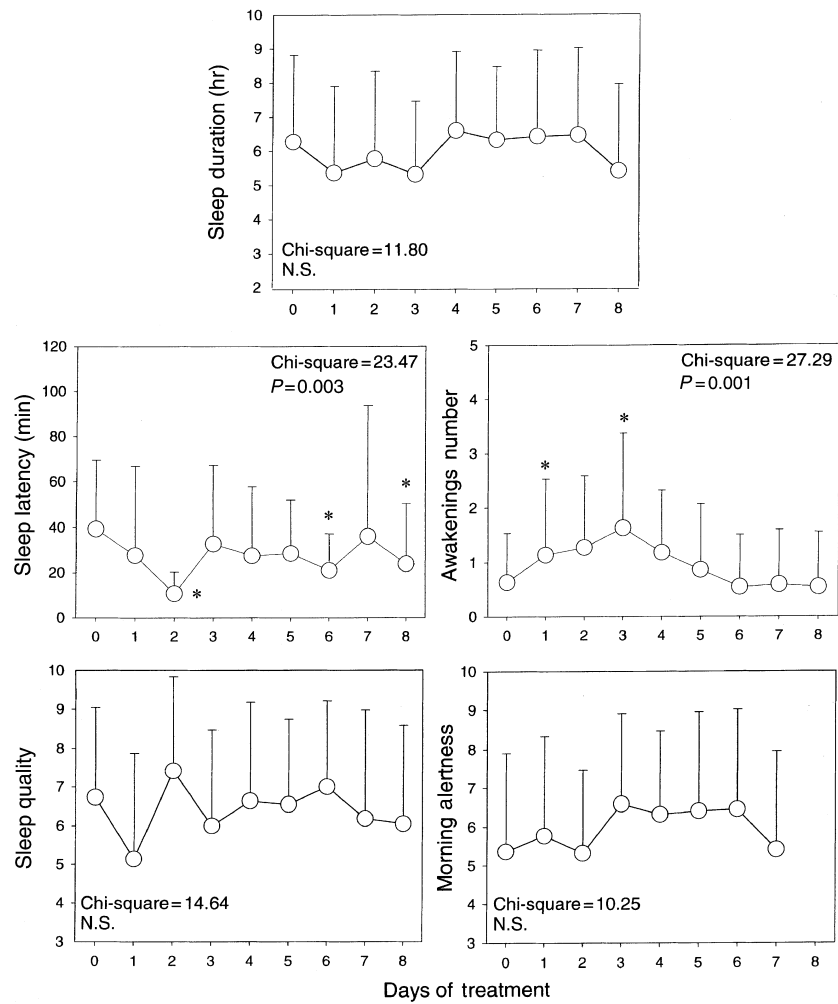


Fig. 2. Sleep log data on sleep duration, sleep latency, sleep quality, number of awakenings and morning alertness obtained from sleep diaries completed by the athletes and their coaches. Days 0 and 1 corresponded to the preflight and flight day from Buenos Aires to Tokyo and days 2–8, the time at Tokyo. Shown are the means \pm S.D. Results were statistically analysed by a Friedman test (nonparametric repeated-measures ANOVA) followed by a Wilcoxon's test. (*) significantly different from day 0; N.S. not significant.

before departure from Buenos Aires (day 0). At this time, 4 out of 22 individuals reported a sleep length less than 5 hr, whereas the range for the remaining 18 was 5.5–9.0 hr. A nonparametric ANOVA generally indicated absence of significant changes as compared with preflight assessment except for number of awakenings (which augmented on days 1 and 3), sleep latency (which decreased on days 2, 6 and 8 at Tokyo).

Fig. 3 shows the correlation of sleep quality and morning alertness with preflight 6-sulphatoxymelatonin excretion when the average values of difference between every day from 1 to 8 and day 0 were plotted. A nonparametric rank correlation analysis indicated significant positive correlation for these two parameters derived from sleep logs, but not for sleep duration, sleep latency or number of sleep awakenings (results not shown).

Representative individual actograms derived from sleep log data are depicted in Fig. 4. Mean resynchronization rate was 2.13 ± 0.88 days. When this value was compared with an expected minimal resynchronization rate of 6 days after a 12-hr flight eastward without any treatment, the differences obtained were significant ($t = -20.38$, $P < 0.0001$).

Discussion

Rapid transmeridian flight air travel, a common reality for modern athletes, has detrimental effects on athletic performance (Winget et al., 1985; Loat and Rhodes, 1989; O'Connor and Morgan, 1990; Hill et al., 1993; Jehue et al., 1993; Recht et al., 1995; Manfredini et al., 1998; Youngstedt and O'Connor, 1999). Therefore, routines designed to resynchronize the circadian rhythm to the new 24-hr environment can help elite athletes in international competitions.

The present study comprised of a multifactorial approach to hasten the resynchronization of a group of elite sports competitors to a 12 time-zone westerly transmeridian flight. To carry out this study a compromise had to be achieved to disturb minimally the players' own schedules and habits. First, we employed exposure to outdoor light attempting to cover symmetrically the phase delay and the phase advance portions of the phase-response curve (PRC) reported for light in humans (Czeisler et al., 1989). Conceivably this would lead to a suppression of circadian rhythmicity and to the sensitization of the circadian clock for additional chronobiological manipulation.

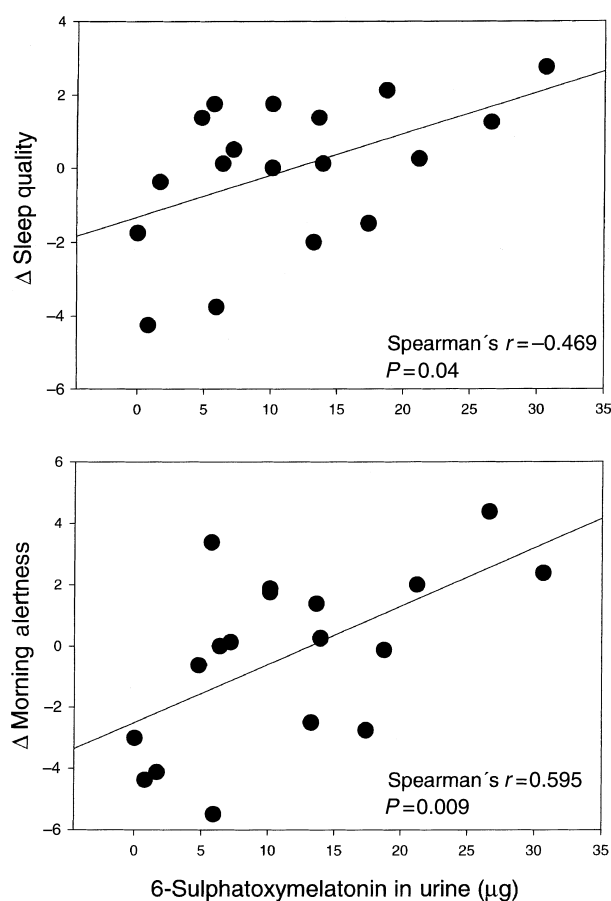
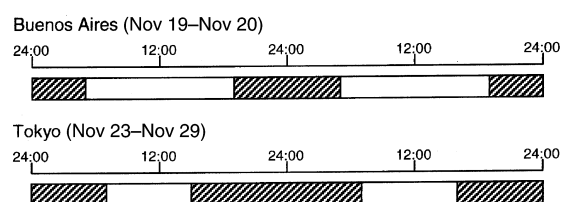


Fig. 3. Sleep quality and morning alertness at Tokyo versus urinary 6-sulphatoxymelatonin excretion (urine collected from 18:00 to 06:00 hrs). Average of differences between every day (from days 1–8) and day 0 (preflight day at Buenos Aires) were plotted against preflight urinary 6-sulphatoxymelatonin. Data were statistically analysed by a nonparametric rank correlation. Spearman's ρ coefficients and their significance are quoted in the Figure.

Secondly, we administered nonphotic stimulation (i.e. physical exercise) that practically coincided with outdoor light exposure as another manipulation tending to mask the circadian oscillator. Thirdly, we gave the athletes melatonin at local bedtime to resynchronize the circadian oscillator to the new time environment. Again in this case, the time of melatonin administration was selected on the basis of introducing the less possible disturbance to daily routine.

Both photic and nonphotic stimuli affect the regulation of the circadian pacemaker (Shiota et al., 1996; Arendt et al., 1997; Klerman et al., 1998; Arendt, 1999; Czeisler and Brown, 1999; Skene et al., 1999; Khalsa et al., 2000; Rimmer et al., 2000). Appropriately timed stimuli induce either a phase-advance or a phase-delay of the circadian clock, according to the timing of administration (Lewy et al., 1998). In the same line, exposure to photic stimuli during (or symmetrically) the subjective night may suppress the circadian clock, the so-called type 0 resynchronization (Czeisler et al., 1989; Jewett et al., 1997; Khalsa et al., 2000).

Phase-shifting effects are known to occur in humans for light pulses (Lewy et al., 1998), physical exercise (Shiota et al.,



Subject A

Subject B

Subject C

Fig. 4. Representative double-plot actograms built from sleep log diaries. 21 November, 2000 was day 0. The game was held on 28 November.

1996; Klerman et al., 1998) and melatonin (Lewy et al., 1998; Skene et al., 1999). The foregoing results indicate that a multifactorial approach that combined the three factors did accelerate the resynchronization of the sleep cycle of a group of elite sports competitors to a 12 time-zone transmeridian flight. Individual actograms performed from sleep log data showed that all subjects became synchronized in their sleep to the local time in 24–48 hr, well in advance to what would be expected in the absence of any treatment. Assessment of sleep quality by comparison of data before and after the transmeridian flight also indicated absence of significant changes in sleep or vigilance as a consequence of the transmeridian flight. To what extent other circadian rhythms became synchronized after the treatment employed is not known. However, as tolerance to jet lag or shift work are frequently associated with a lack or relatively minor internal desynchronization of circadian rhythms (Reinberg et al., 1989) an accelerated resynchronization of other circadian rhythms would be expected.

Most transmeridian travellers going in a westerly direction have less severe jet lag as compared with when they travel east. This was one of the reasons to design the trip for the athletes in the present study. It must be noted however,

that such a difference in flying west or east tends to be minimized by a 12 time-zone flight producing a 180° shift in local Zeitgebers. Whether the multifactorial regimen hereby reported would work as effectively in individuals travelling easterly should be further explored.

In the sample of individuals studied some particularities became apparent. Sleep duration showed a high variability and was relatively short before leaving Buenos Aires. Indeed, 4 out of the 22 subjects reported a sleep length of less than 5 hr. This might have an impact on the ability to detect changes after the trip in these individuals and this would influence in an unknown way the results reported herein. In any event, during the first days at Tokyo the players performed in a way not different to that routinely observed in Buenos Aires. Because of the restrictions of the study no information could be obtained on the lifestyle of the subjects before the trip. To what extent this explains the very high variability in 6-sulphatoxymelatonin excretion observed in the sample warrants additional investigation.

A positive correlation was found between the preflight melatonin production rates, evaluated by measuring urinary 6-sulphatoxymelatonin excretion, and sleep quality and morning alertness after flight. As initially suggested by Aschoff, the ability to adjust rapidly to a phase-shift is associated with having small amplitude for certain circadian rhythms, remarkably body temperature (Aschoff, 1978). However, persons who possess a weak circadian time structure, as revealed by low-amplitude of body temperature rhythm, are more prone to develop biological intolerance to shift work (Andlauer et al., 1979; Smolensky and Reinberg, 1990) and presumably to jet lag. Further analysis of the validity of a high amplitude of the circadian rhythm in melatonin production rate to predict a better response to the multifactorial resynchronization strategy hereby employed remains to be done.

It has been known for a long time that a light stimulus of a critical strength applied at a critical circadian phase could essentially stop the human circadian clock by resetting the circadian oscillator close to a phaseless position at which the amplitude of circadian oscillation is zero, i.e. type 0 resynchronization (Czeisler et al., 1989; Jewett et al., 1997; Khalsa et al., 2000). Indeed, exposure of humans to cycles of bright light, centered on the time at which the human circadian pacemaker is most sensitive to light-induced phase shifts, can markedly attenuate or reduce endogenous circadian amplitude. We took advantage of this situation to obtain an almost immediate synchronization to the local time by superimposing the administration of the chronobiotic agent melatonin at local bedtime (Dawson and Armstrong, 1996; Cardinali and Pévet, 1998).

With few exceptions (Spitzer et al., 1999), a compelling amount of evidence indicates that melatonin is useful for ameliorating 'jet lag' symptoms in air travellers (Petrie et al., 1989; Clausturat et al., 1992; Lino et al., 1993; Arendt et al., 1997; Czeisler, 1997; Arendt, 1999; Samel, 1999; Skene et al., 1999; Edwards et al., 2000; Takahashi et al., 2000). The single published study on melatonin use in athletes comprised of the examination of body temperature rhythm in 12 athletes taking a similar dose of melatonin as that herein employed after an eastward transmeridian flight to an international competition (Manfredini et al., 2000).

The authors concluded that individually adjusted dosage schedules are needed to avoid potential undesirable consequences of melatonin administration. Our present study indicates that by combining melatonin with an appropriate schedule of light exposure and physical exercise, the efficacy of the treatment can be significantly improved.

Besides the environmental light-dark cycle, the timing of behavioural events (activity, social interactions) has been reported to contribute to entrainment of human circadian rhythms. For example, in cockpit crewmembers investigated before, during and after jet travel, outdoor exercise had a significant effect in hastening the resynchronization to a new environment (Shiota et al., 1996). To what extent physical activity employed in the present resynchronization schedule (a 3-hr bout of moderate-intensity exercise at two times of the day coinciding with outdoor light exposure) is a principal or secondary factor in entrainment cannot be discerned from the present study. However, available data indicate that the environmental light-dark cycle is the principal factor to entrain human circadian rhythms (Khalsa et al., 2000; Rimmer et al., 2000).

In summary, the combination of melatonin treatment, an appropriate environmental light schedule and timely applied physical exercise can be useful to help elite athletes to overcome the consequences of jet lag. Further studies are needed to evaluate the relative importance of each manipulation to counteract the sequels imposed by international itineraries in travelling athletes.

Acknowledgments

This study was supported by Elisium S.A., Buenos Aires, the Agencia Nacional de Promoción Científica y Tecnológica, Argentina (PICT 6153), University of Buenos Aires (TM 07), Ministerio de Salud, and Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina (PIP 4156).

References

- ANDLAUER, P., A. REINBERG, L. FOURRE, W. BATTLE, G. DUVERNEUIL (1979) Amplitude of the oral temperature circadian rhythm and the tolerance to shift-work. *J. Physiol. (Paris)* 75:507-512.
- ARENDT, J. (1998) Jet lag. *Lancet* 351:293-294.
- ARENDT, J. (1999) Jet lag and shift work: (2). Therapeutic use of melatonin. *J. R. Soc. Med.* 92:402-405.
- ARENDT, J., C. BOJKOWSKI, C. FRANEY, J. WRIGHT, V. MARKS (1985) Immunoassay of 6-hydroxymelatonin sulfate in human plasma and urine: abolition of the urinary 24-hour rhythm with atenolol. *J. Clin. Endocrinol. Metab.* 60:1166-1173.
- ARENDT, J., D.J. SKENE, B. MIDDLETON, S.W. LOCKLEY, S. DEACON (1997) Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J. Biol. Rhythms* 12:604-617.
- ASCHOFF, J. (1978) Features of circadian rhythms relevant for the design of shift schedules. *Ergonomics* 21:739-754.
- CARDINALI, D.P., P. PÉVET (1998) Basic aspects of melatonin action. *Sleep Med. Rev.* 2:175-190.
- CLAUSTURAT, B., J. BRUN, M. DAVID, G. SASSOLAS, G. CHAZOT (1992) Melatonin and jet lag: confirmatory result using a simplified protocol. *Biol. Psychiatry* 32:705-711.
- CZEISLER, C.A. (1997) Commentary: evidence for melatonin as a circadian phase-shifting agent. *J. Biol. Rhythms* 12:618-623.

- CZEISLER, C.A., E.N. BROWN (1999) Commentary: models of the effect of light on the human circadian system: current state of the art. *J. Biol. Rhythms* 14:538–543.
- CZEISLER, C.A., R.E. KRONAUER, J.S. ALLAN, J.F. DUFFY, M.E. JEWETT, E.N. BROWN, J.M. RONDA (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science* 244:1328–1333.
- DAAN, S., C.S. PITTENDRIGH (1976) A functional analysis of circadian pacemaker in nocturnal rodents: II. The variability of phase response curves. *J. Comp. Physiol. A* 106:253–266.
- DAWSON, D., S.M. ARMSTRONG (1996) Chronobiotics – drugs that shift rhythms. *Pharmacol. Ther.* 69:15–36.
- DEACON, S., J. ARENDT (1996) Adapting to phase shifts, I. An experimental model for jet lag and shift work. *Physiol. Behav.* 59:665–673.
- EDWARDS, B.J., G. ATKINSON, J. WATERHOUSE, T. REILLY, R. GODFREY, R. BUDGETT (2000) Use of melatonin in recovery from jet lag following an eastward flight across 10 time-zones. *Ergonomics* 43:1501–1513.
- GHERARDIN, T. (1999) Jet lag. A problem for ‘long haul’ travellers. *Aust. Fam. Physician.* 28:833.
- HILL, D.W., C.M. HILL, K.L. FIELDS, J.C. SMITH (1993) Effects of jet lag on factors related to sport performance. *Can. J. Appl. Physiol.* 18:91–103.
- JEHUE, R., D. STREET, R. HUIZENGA (1993) Effect of time zone and game time changes on team performance: National Football League. *Med. Sci. Sports Exerc.* 25:127–131.
- JEWETT, M.E., D.W. RIMMER, J.F. DUFFY, E.B. KLERMAN, R.E. KRONAUER, C.A. CZEISLER (1997) Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. *Am. J. Physiol.* 273:R1800–R1809.
- KHALSA, S.B.S., M.E. JEWETT, J.F. DUFFY, C.A. CZEISLER (2000) The timing of the human circadian clock is accurately represented by the core body temperature rhythm following phase shifts to a three-cycle light stimulus near the critical zone. *J. Biol. Rhythms* 15:524–530.
- KLERMAN, E.B., D.W. RIMMER, D.J. DIJK, R.E. KRONAUER, J.F. RIZZO, C.A. CZEISLER (1998) Nonphotic entrainment of the human circadian pacemaker. *Am. J. Physiol.* 274: R991–R996.
- LEWY, A.J., V.K. BAUER, S. AHMED, K.H. THOMAS, N.L. CUTLER, C.M. SINGER, M.T. MOFFIT, R.L. SACK (1998) The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiol. Int.* 15:71–83.
- LINO, A., S. SILVY, L. CONDORELLI, A.C. RUSCONI (1993) Melatonin and jet lag: treatment schedule. *Biol. Psychiatry* 34:587.
- LOAT, C.E., E.C. RHODES (1989) Jet lag and human performance. *Sports Med.* 8:226–238.
- MANFREDINI, R., F. MANFREDINI, C. FERSINI, F. CONCONI (1998) Circadian rhythms, athletic performance, and jet lag. *Br. J. Sports Med.* 32:101–106.
- MANFREDINI, R., F. MANFREDINI, F. CONCONI (2000) Standard melatonin intake and circadian rhythms of elite athletes after a transmeridian flight. *J. Int. Med. Res.* 28:182–186.
- O’CONNOR, P.J., W.P. MORGAN (1990) Athletic performance following rapid traversal of multiple time zones. *A Rev. Sports Med.* 10:20–30.
- PETRIE, K., J.V. CONAGLEN, L. THOMPSON, K. CHAMBERLAIN (1989) Effect of melatonin on jet lag after long haul flights. *BMJ.* 298:705–707.
- RECHT, L.D., R.A. LEW, W.J. SCHWARTZ (1995) Baseball teams beaten by jet lag. *Nature* 377:583.
- REINBERG, A., Y. MOTOHASHI, P. BOURDELEAU, Y. TOUITOU, J. NOUGUIER, J. NOUGUIER, F. LEVI, A. NICOLAI (1989) Internal desynchronization of circadian rhythms and tolerance of shift work. *Chronobiologia* 16:21–34.
- RIMMER, D.W., D.B. BOIVIN, T.L. SHANAHAN, R.E. KRONAUER, J.F. DUFFY, C.A. CZEISLER (2000) Dynamic resetting of the human circadian pacemaker by intermittent bright light. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279:R1574–R1579.
- SAMEL, A. (1999) Melatonin and jet lag. *Eur. J. Med. Res.* 4: 385–388.
- SHIOTA, M., M. SUDOU, M. OHSHIMA (1996) Using outdoor exercise to decrease jet lag in airline crewmembers. *Aviat. Space. Environ. Med.* 67:1155–1160.
- SKENE, D.J., S.W. LOCKLEY, J. ARENDT (1999) Use of melatonin in the treatment of phase shift and sleep disorders. *Adv. Exp. Med. Biol.* 467:79–84.
- SMOLENSKY, M.H., A. REINBERG (1990) Clinical chronobiology: relevance and applications to the practice of occupational medicine. *Occup. Med.* 5:239–272.
- SPIZZER, R.L., M. TERMAN, J.B. WILLIAMS, J.S. TERMAN, U.F. MALT, F. SINGER, A.J. LEWY (1999) Jet lag: clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. *Am. J. Psychiatry* 156:1392–1396.
- TAKAHASHI, T., M. SASAKI, H. ITOH, M. OZONE, W. YAMADERA, K. HAYSHIDA, S. USHIJIMA, N. MATSUNAGA, K. OBUCHI, H. SANO (2000) Effect of 3 mg melatonin on jet lag syndrome in an 8-h eastward flight. *Psychiatry Clin. Neurosci.* 54:377–378.
- WATERHOUSE, J., T. REILLY, G. ATKINSON (1997) Jet lag. *Lancet* 350:1611–1616.
- WINGET, C.M., C.W. DEROSHIA, D.C. HOLLEY (1985) Circadian rhythms and athletic performance. *Med. Sci. Sports Exerc.* 17:498–516.
- YOUNGSTEDT, S.D., P.J. O’CONNOR (1999) The influence of air travel on athletic performance. *Sports Med.* 28:197–207.