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Pharmacology and the travelling athlete

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1. INTRODUCTION

Prior to almost every recent Olympic games, there has been concern about particular environmental stresses that may confront the athletes. This concern is reflected in the publication of studies on the effects of altitude [1] and air pollution [2] on athletic performance which preceded the games in Mexico and Los Angeles, respectively. In 2000, athletes from the European, African and American continents will be travelling to Sydney to compete in the Olympics. Here, these athletes will not only be exposed to high environmental temperatures, but may have to cope with long-haul flights before competing.

Foreign travel makes great demands on team managers, athletes and coaches, whether they are planning trips abroad for single competition or a prolonged tour. Before travelling to some countries, a vast surveillance exercise is called for to glean information about the culture and customs of the host country, the immunization necessary, climatic factors including temperature, seasonal variations in climate, altitude and so on. Travel *within* the same country may be associated with motion sickness or even some degree of mild jet lag [3].

This review is concerned with the specific effects of transmeridian travel rather than the very transient problems of general travel fatigue and motion sickness. There is a wealth of literature [4] on the latter problem for readers to consult. Before any proposed pharmacological aids to dealing with jet lag can be discussed, the principles of chronobiology and the specific problems associated with rapid transport across time zones may be considered.

2. CHRONOBIOLOGY

2.1. Definition of terms

Chronobiology is concerned with investigating and objectively quantifying the mechanisms of biological rhythms. A biological rhythm is a sequence of events which, in a steady state, repeats itself in time in the same order and in the same interval [5]. Most rhythms can be represented by a sine-wave like the 24-hour body temperature curve shown in Figure 1. The time required to complete one cycle is described as the period of a rhythm. Rhythms with a period of 20-28 hours are termed circadian. Those rhythms with periods less than 20 hours (e.g. the 90 minute cycle of sleep stages) and greater than 28 hours (e.g. the menstrual cycle)

are known as ultradian and infradian, respectively. The mean value of a rhythm is described as the mesor. The amplitude of a rhythm is the difference between the mesor and the highest point of a cosine curve fitted to the data. The location in time of the peak of a rhythm is termed the acrophase which is usually expressed in absolute units of time e.g. minutes, hours, days, weeks or years, and relative to either an environmental or physiological reference point such as midnight (Figure 1) or the onset of melatonin secretion (Figure 2).

2.2. Human circadian rhythms

Circadian rhythms have been the most extensively investigated fluctuations and have the farthest reaching implications for humans. Circadian rhythms in physiological parameters are influenced by rhythmic changes in human behaviour and the environment over a period of 24 hours [5]. For example, human society generally exhibits diurnal wakefulness and activity, and nocturnal inactivity and sleep. Fluctuations such as these are termed "exogenous components" to physiological rhythmicity. Circadian rhythmicity is not fully dependent upon exogenous factors, but has also an "endogenous component" (colloquially referred to as the biological- or body-clock). Thus, rhythmicity persists if an individual remains awake for several days at a constant level of activity.

The inherent *properties* of the body clock have been investigated in studies on "temporal isolation". This refers to environmental conditions which do not fluctuate, such as a natural cave or a specially designed isolation chamber. Wever [6] found that the period of circadian rhythms deviates slightly but consistently from 24 hours to approach 25 hours. Therefore, the endogenous clock will progressively lag behind exogenous fluctuations as time spent in isolation increases up to 12 days. It thus "free runs". The "body clock" is believed to be situated in the paired suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The existence of a second biological clock has been speculated since in temporal isolation, the sleep-wake cycle and body temperature rhythm sometimes dissociate [6]. Endogenous rhythms are synchronised or "entrained" to the normal 24 hour environment by zeitgebers ("time givers"), the most important of which are the light-dark cycle, social influences and the sleep-wake cycle. Light is believed to act as a zeitgeber to the body clock via the transmission of photic information along the retinohypothalamic tract (a neural pathway connecting the retinae with the SCN). Light also suppresses the production of melatonin by the pineal gland [7] which is believed to provide feedback information to the suprachiasmatic nuclei, thereby acting as an "internal zeitgeber".

The majority of the components of sports performance (e.g. reaction time, flexibility, muscle strength, short-term peak power output) vary with time of day in a sinusoidal manner and peak in the early evening, close to the daily maximum in body temperature [8,9]. Short-term memory [10] and prolonged submaximal exercise performance carried out in hot conditions [11] show peak-times in the morning. Post-lunch transient declines are evident with performance variables such as muscle strength.

3. TRANSMERIDIAN FLIGHT DYSRHYTHMIA (JET LAG)

The feelings of disorientation encountered as a result of crossing time zones are known as jet lag. Symptoms include fatigue and general tiredness, inability to sleep at night, loss of concentration, loss of drive, headaches and general malaise [5]. Sufferers may have bizarre

lapses in mental attention and unusual errors in short-term memory. These problems are a consequence of disrupting the body's normal rhythms as a result of rapid transitions across multiple time-zones. Such desynchronisation of rhythms is similar in principle to that which occurs in nocturnal shift-work employees on transfer to night shifts. A difference is that travellers across time-zones must fit in with all aspects of local time in the new environment. This is especially important in athletes who generally want to maintain their training habits or continue a systematic build-up for a forthcoming contest.

Following a journey across multiple time zones the body's rhythms at first retain the characteristics of their point of departure. The new environment soon forces new influences on these cycles, the main factors being the time of sunrise and onset of darkness. The body attempts to adjust to this new context but core temperature is relatively slow in doing so. As a rough guide it can take up to one day for each time zone crossed for body temperature to adapt completely [9]. Until the whole spectrum of biological rhythms adjusts to the new local time, thereby becoming re-synchronised, the performance of exercise may be below par.

Allowing for individual differences, the severity of jet lag is affected by a variety of factors. In general, the greater the number of time zones crossed, the more difficult it is to cope [5]. The severity of symptoms may be worse 2-3 days after arrival than on the day immediately following disembarkation. Symptoms then gradually abate, but can still be acute at particular times of day. Jet lag is generally worse when travelling eastwards compared to westwards [12]; the endogenous body clock cycles at a pace slower than 24 hours [6], and so it is easier to delay circadian rhythms to the new environment to the west than to advance them after arrival in a new environment to the east.

Much of the evidence summarised so far on jet lag has been based on laboratory studies and physiological variables e.g. heart rate, body temperature. The effects of transmeridian travel on athletic performance have been reviewed previously [13]. Despite the fact that many aspects of performance are linked to the slowly adjusting rhythm in body temperature, O'Connor and Morgan [13] concluded there was little scientific evidence to support the notion that transmeridian travel affects athletic performance. Many studies on jet lag and athletic performance have been badly administered. To study, chronobiologically, the influence of time-zone travel on sports performance, athletes should be tested at several times of day for several days after a flight. Alternatively, phase shifts of the sleep-wake cycle could be simulated in the laboratory. Recently, such studies have been performed and the results suggest that physical performance worsens and takes time to adjust following a westward flight across 5 time zones [14] and after simulated phase-shifts of the sleep-wake cycle [15].

4. CHRONOBIOTICS FOR THE TRAVELLING ATHLETE

As interest in chronobiology has grown, subareas of the science have emerged. Chronopharmacology is concerned with time-dependent changes in the action of drugs and can be further divided into chronotherapy, chronoparmacokinetics and chronotoxicity [16]. In this review, we are concerned with "chronobiotics" which are drugs that have a direct influence on a biological rhythm, particularly in changing its phase. Experiments have shown that the size and even direction of shift of a circadian rhythm depend on the time of administration of the chronobiotic. This action of a drug on the timing of a circadian rhythm can be represented by a "phase-response curve", an example of which is shown in Figure 2.

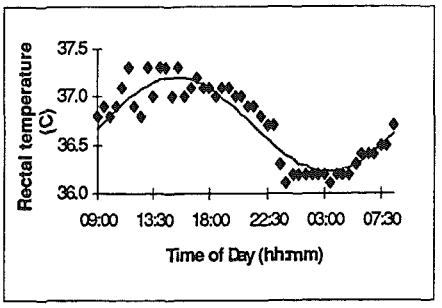

Figure 1.
The circadian rhythm of body temperature
Raw data shown with cosine curve fitted
Measured in our laboratories on author S.W. with an ambulatory recorder. Mesor=36.8 °C
Amplitude=0.5 °C, Acrophase=16:00 hours.

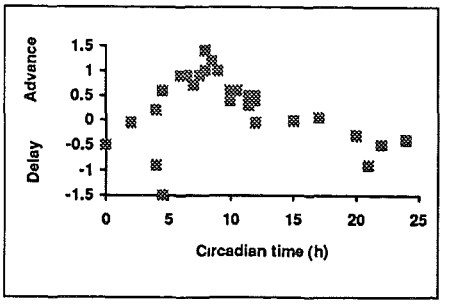

Figure 2.
The phase-response curve for melatonin.
The direction and degree of phase change of the melatonin onset time depends on the time of ingestion. Circadian time=0 refers refers to about 07:00 hours (real time) [17]

Redfern [18] stressed the unlikelihood of chronopharmacologists developing a panacea-like "jet lag pill", since the circadian system is so complicated with multiple input and output signals to and from the body clock(s). However, three possible sites of action for a chronobiotic drug were proposed: (i) the transmission of zeitgeber signals to the body clock(s), (ii) the transmission of information between body clocks (assuming there is more than one), (iii) the transmission of information between the body clock(s) and the overall rhythms.

Dawson and Armstrong [19] listed many classes of drugs that have the capacity to modify the circadian system, including cholinergics, corticosteriods, antidepressants and antimanics. However, attention will be directed to those drugs that are not banned in most sports; the benzodiazepines and melatonin.

4.1. Benzodiazepines

One of the major zeitgebers in humans is the timing of the sleep-wake cycle and all its concomitants e.g. feeding, activity [5]. Hypnotics could reinforce this cycle at the new local time and this could mediate faster entrainment [20]. Benzodiazepines easily pass through the blood-brain barrier. The sedative and hypnotic properties of the benzodiazepines are thought to occur through the binding to GABAa receptors in the thalamocortical neuronal network [21].

There are also GABAa receptors in the SCN which may suggest a direct effect of benzodiazepines on the body clock. In support of this notion, Turek and Losee-Olsen [22] successfully induced a phase shift in the activity rhythm of hamsters with the benzodiazepine, triazolam. Faster entrainment rates for the activity rhythm following a shift in the light-dark cycle have also been reported when other benzodiazepines are administered to hamsters [23,24]. It is stressed that, in hamsters, unlike in humans, benzodiazepines *increase* locomotor activity. Indeed, it is the increased activity itself which is thought to mediate phase shifts rather than any direct pharmacological effect on the body clock [25]. Besides, the doses employed in the hamster studies were far higher than normal human doses [19] and the results have not been replicated in other animal species [26].

It appears that benzodiazepines do aid sleep in humans following transmeridian travel [21], although there have been reports of negative findings with triazolam [27]. In practice, it is not sending athletes to sleep that is the problem but rather making sure that they are fully awake and alert when they compete. Most of the benzodiazepines are associated with residual effects on alertness and psychomotor performance [28] which would be disastrous for competitions during the day. For these reasons, when high levels of mental and physical performance are required, individuals should be very cautious about the use of sleeping tablets.

Temazepam may be less associated with residual effects on performance than other benzodiazepines [28], since its half-life is only 2-8 hours compared to diazepam's 24-48 hours and it has a low receptor affinity [21]. Reilly *et al.* [14] examined whether temazepam improved the adaptation to a westerly flight across five time zones. Subjects comprised eight members of the British men's gymnastics squad, aged 18-30 years, and nine members of the British Olympic Association's support staff, aged 24-55 years (4 females, 5 males). Subjects were pair-matched for age, sex and athleticism (apart from one person) and assigned to either the treatment (n=9) or placebo (n=8) group. All subjects travelled from U.K. and arrived at the British Olympic Training camp at Tallahassee, Florida at approximately 22:00 hours local time. A test battery was administered to the subjects at 07:00, 12:00, 17:00 and 21:00 hours on the first full day of arrival (this was designated day one) and then on every other day (day 3, day 5 and day 7). Immediately before retiring to bed on days 1, 2 and 3, subjects ingested either 10 mg of temazepam or a placebo. This meant that day 1 was the baseline day on which the test battery was administered without any treatment or placebo intervention. Subjective jet lag reduced from 4.6 units to zero, and sleep quality improved by 2.0 units from day 1 to day 5 in both the control and experimental groups, after which no further alterations were noted. Subjective jet lag, tympanic and oral temperature, left and right grip strength and choice reaction time all showed post-flight day and time of day interactions. On day 1, these variables deteriorated as the day progressed to the worst recorded values. On days 3, 5 and 7, circadian variations with the conventional peaks in the early evening and peak-trough differences of about 10% were evident. The ingestion of temazepam did not influence any of these findings.

4.2. Melatonin

In normal circumstances, melatonin secretion from the pineal gland is a very reliable marker of the body clock and is secreted into the blood stream between about 21:00 and 07:00 hours [7]. Melatonin is thought to influence the circadian system in two ways. First, melatonin may amplify the signal from the SCN to the overall circadian rhythms. Second, melatonin has been viewed as a key factor in modulating the zeitgeber-effects of bright light [19].

Like the benzodiazepines, phase shifting effects of exogenous melatonin have been observed on the circadian activity rhythms of animals [29]. Unlike the benzodiazepines, a phase response curve for melatonin has been reported in humans [17], although the delaying properties of melatonin are very slight (Figure 2). Melatonin has been shown to reduce subjective symptoms of jet lag after flights in easterly and westerly directions [7]. Melatonin was originally considered as a true chronobiotic i.e. a drug which acts directly on the body clock but it is also a mild hypnotic and lowers body temperature [30]. Therefore, melatonin may improve sleep through its hypnotic action and temperature-lowering properties, which in turn improves mood, alertness and entrainment (through the sleep-wake cycle as a strengthened zeitgeber).

Despite uncertainty over the mechanisms of melatonin, oral administration of the hormone is believed to be the best pharmacological "cure" for jet lag to date. However, there is a major caveat from an athlete's perspective. If melatonin does have a hypnotic action, like the benzodiazepines, it may induce undesirable residual effects, especially if taken during the day. A large dose of melatonin (240 mg) administered to subjects at midday was found by Lieberman *et al.* [31] to increase reaction time and induce drowsiness and sleep. The same research group found decreased oral temperature, number of correct responses in auditory vigilance and vigour as well as increased reaction time after administration of much lower doses (10 mg) of melatonin [30]. Even if competitive events are scheduled after melatonin administration has ceased, the athlete's post-flight training may still be negatively affected while ingesting melatonin which could have carry-over effects to competition. Besides, melatonin has no licence in Europe at present. It is available from health food retailers in the U.S.A., but the purity of the drug would be uncertain and the instruction for use to "ingest the drug before bed-time" is not necessarily correct bearing in mind the phase-response curve (Figure 2). This instruction may be relevant, however, if melatonin was to used solely for its hypnotic effects.

5. NON-PHARMACOLOGICAL AIDS

5.1. Bright light

Bright light (that is, of an intensity found naturally but not normally indoors) appears to be a much more potent zeitgeber than melatonin in humans and can adjust the body clock [19]. The timing of exposure to it is crucial [32] and is the opposite of that for melatonin ingestion; thus bright light in the morning (05:00–11:00) on body time advances the clock and bright light in the evening (21:00–03:00) on body time delays it. As a supplement to this treatment there are also times when light should be avoided (those times which produce a shift of the body clock in a direction opposite to that desired); at such times that it would be appropriate for melatonin (the "dark pulse") to be taken, if melatonin works by adjusting the body clock and if the immediate hypnotic effects of melatonin are unimportant (see above). Table 1 gives times when light should be sought or avoided after different time–zone transitions.

Even though "bright light" is of an intensity normally not achieved in domestic or interior lighting, light boxes and visors that produce a light source of sufficient intensity are now available commercially.

5.2. Social factors and activity

Since outdoor lighting is the obvious choice of bright light, it would be reasonable, therefore, to consider training for exercise outdoors when light is required, and to relax indoors when it should be avoided. This raises the question whether physical exercise and inactivity can, in some way, substitute for light and dark, respectively. Current results [33,34] suggest that "pulses" of activity can phase-shift circadian rhythms, although more research is needed to determine whether a phase-response curve for activity exists in humans. In practice, to combine exposure to bright light and exercise, and to combine dim light and relaxation, would seem advisable for promoting adjustment to the new time zone. The timing of this behaviour may be important. For example, for the first few days after a flight to Sydney from

the U.K. (westerly flight across 10-11 time zones), outdoor training in the evening would be recommended and training before noon should be avoided (Table 1).

Table 1
The use of bright light to adjust the body clock after time–zone transitions.

	Bad local times for exposure to bright light	Good local times for exposure to bright light
Time zones to the west		
4 hours	01:00–07:00*	17:00–23:00†
8 hours	21:00–03:00*	13:00–19:00†
10 hours	19:00–01:00*	11:00–17:00†
Time zones to the east		
4 hours	01:00–07:00†	09:00–15:00*
8 hours	05:00–11:00†	13:00–19:00*
10 hours	07:00–13:00†	15:00–21:00*

*Will advance the body clock; †Will delay the body clock

5.3. Diet

It has been argued that high–protein breakfasts promote alertness and that high–carbohydrate evening meals promote sleep [35]. The theoretical grounds for this include the effects upon plasma amino acids that such meals would have and, thence, the uptake of the amino acids into the brain, their incorporation into neurotransmitters and the release of the neurotransmitters. High protein meals undoubtedly raise plasma tyrosine, but whether this promotes the release of catecholamines by the activating systems of the brain, and so promotes alertness, is less clear. Similarly, high–carbohydrate meals promote the concentration of plasma tryptophan, but whether this stimulates the raphe nucleus and sleep also is uncertain [36]. Even so, a variant of this proposal has been marketed. It consists of two types of pills, one to be taken in the morning and the other in the evening. Each pill is a mixture of substances, the morning pill containing tyrosine and the evening one, tryptophan. The accompanying literature does not enable a judgement to be made on the scientific evaluation of these preparations.

6. CONCLUSIONS

It appears that benzodiazepines and melatonin affect the circadian system and induce phase shifts in circadian rhythms, although the mechanisms for these changes are unclear. Only the effects of temazapam have been studied in athletes and results suggest that administration of the drug does not improve jet lag symptoms including the declines in performance following transmeridian travel. Both the benzodiazepines and melatonin are associated with adverse effects on alertness and psychomotor performance. For these reasons, and in view of the lack of adequate research using physically active subjects and performance measures as dependent

variables, we advise the competitor not to administer these drugs after crossing multiple time-zones for competition. More promising coping strategies for transmeridian travel may centre around careful scheduling of the exposure to bright light and participation in physical exercise bouts. More research work is needed to identify how the phase shifting effects of bright light and exercise interact in humans.

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Discussion: Pharmacology and the Travelling Athlete

K.A. Perkins:

I mentioned earlier the phenomenon of "state dependent performance", and there was some research about 20 years ago on animals by Frank Holloway at the University of Oklahoma that found a similar effect with performance and time of day. It was an ultradian rhythm, so animals tested 12, 24, 36, 48 hours after initially learning a complex escape task performed optimally. Those tested at 6, 18, 30, 42 hours performed poorly, regardless of the time of day at which they learned the task. I guess what it suggests is that, just as you want the drug state to be the same, you may want even the time of day to be the same, such that if you are running a marathon in the morning, focus your training in the morning, etc. Whether this is relevant to performance in humans, I do not know.

G. Atkinson:

I am not aware of any work dealing specifically with the approach that you mention. The subjects in the studies I showed were used to taking benzodiazepines and the subjects in the melatonin study had used melatonin before. So, it was not as if that was a new situation to them and they had not used those drugs before. We monitored the performance for a number of days and the effects were consistent over those days.

J.R. Barbany:

It is popularly assumed that the effects of jet lag are different when you travel with the sun or against the sun. Are there are objective proofs about that?

G. Atkinson:

Yes, that effect is definitely there. Jet lag appears to be worse after eastward travel than it does after westward travel. The reasons that have been put forward for this have to do with the body clock running slow in isolation studies. As I mentioned, the body clock runs to a 25 or even a 26 hour day in the absence of environmental synchronizers. So when you are travelling westward you are working with the body clock and effectively putting more hours into the day. When you are travelling eastward you are working against the natural period of the body clock and it could be likened to taking hours off the day.

D.R. Mottram:

Have you an explanation for the all or none effect with melatonin. You have indicated with your dose response relationship that all of the doses seem to produce the same response. Could it be that even the lowest dose -10 milligrams- was in the maximum region of the dose response relationship, or is it a question of the purity of the substance?

G. Atkinson:

I think I would definitely go with the former, that even 10 milligrams is far too high, compared to the physiological concentrations you get in the plasma. These claims of exorbitant doses are totally irresponsible in view of the lack of research on exogenous melatonin administration.

N.T. Cable:

If exercise can phase shift and rhythm, is there any evidence to suggest that athletes who chronically exercise have a less stable rhythm than people who do not exercise at all?

G. Atkinson:

I think stability is another question, and there is evidence from one study with athletes. When the athletes exercised in the morning for a three week period, and they exercised also in the late afternoon for a three week period, there was a one to two hour difference in their circadian rhythms when they were measured under bed rest conditions, so all of the exogenous effects were removed. So that is suggesting that exercise at different times of day is affecting the body clock itself. As for stability of rhythms, we have found that a number of athletes seem to have higher amplitude rhythms than sedentary subjects and that this observation may be due to a less disturbed sleep. We usually find that the first measure taken after sleep is generally lower compared to the mean level over the 24 hours in athletes than sedentary subjects. Now, chronobiologists argue what the implications of that are. Some say it might mean that people with more stable rhythms cope better with fastly rotating shift work.

B. Ekblom:

I think there is experience that you learn to cope with jet lag over the years. Can you comment on that?

G. Atkinson:

I think that could be a definite factor. What we have found with the athletes travelling to the training camp in Tallahassee is that the first year that they went they seemed to suffer quite badly from the jet lag. Consequently, all sort of chronobiological information was given out on not to take naps during the day, the correct times to be exposed to bright light, the correct times to take exercise and so on, and we did find that the athletes seemed to suffer less from jet lag that second time they went over to Tallahassee. However, in old age, it is known that jet lag effects are worse.

D.P.M. MacLaren:

I presume that in considering the effects of melatonin we should take into account that what is administered adds to the normal concentrations in the plasma, and this varies during the day. If, say, melatonin has its greatest influence when you take it at ten o'clock at night rather than ten o'clock in the morning, and then you shift time zones twelve hours away and take it at the 'new' ten o'clock at night. Your body clock is twelve hours out of synchronisation, therefore you have got a double influence.

G. Atkinson:

Yes, definitely. The first response curve that I showed is derived relative to body clock time and so it gets extremely complicated how to work out the optimal timing of the melatonin dose, in that you may be taking it a time of day (body clock time) that is in the daytime (real time) and you will of course induce these immediate hypnotic effects which of course could be disastrous for any training that you are doing prior to a major competition.

F. Brouns:

People who work at day and go on the night shift, have a disturbance of their sleeping rhythm activity, but after a couple of days they get adapted. This lead to my question. Athletes who go to foreign countries generally minimize the time for acclimation for cost reasons. Do you think it would be possible to be proactive and to shift the daily rhythm, let us say, to do "night shift" early morning or late evening training sessions and thereby shift the daily pattern before travelling to the other country?

G. Atkinson:

The small amount of work that has been done on pre-adjustment of circadian rhythms suggests that it does not help much. It could have a deleterious effect especially if the athlete is trying to get in some last minute high intensity training. I do not think I would advise an athlete to try to adopt the destination time zone before the flight. The general advice is just to adopt the new zone's time as soon as one boards the plane.

O.I. Aruoma:

I have a comment to make concerning our work. Russel Reiter and his co-workers published and interesting paper recently suggesting that melatonin confers partial protection against swimming imposed oxidative stress on the liver and skeletal muscle of male Sprague-Dawley rats. In both tissues melatonin pretreatment abated the decreases in GSH concentrations and decreased GS/GSSG ratios. Indeed melatonin is being increasingly promoted as a treatment for "jet lag" and insomnia and has been suggested to act as an antioxidant *in vivo*. Our recent work showed melatonin to be an excellent scavenger of peroxyl radicals -the trichloromethylperoxyl radicals generated by pulse radiolysis with a calculated rate constant 2.7×10^8 $M^{-1}s^{-1}$. Unfortunately this was not reflected in its ability to inhibit lipid peroxidation. This data may have been confounded by solubility restrictions. Melatonin reacted well with the oxidant hypochlorous acid but the high relative concentrations needed suggested that the cytoprotective effects of melatonin may not be mediated by direct reactive oxygen species scavenging. I think that there is a case for urgent investigations of the biological effects of melatonin with respect to modulation of baseline oxidative status in the context of athletes.