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Melatonin has no effect on tolerance to uncompensable heat stress in man

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Abstract This study examined whether a 5 mg dose of melatonin induced a lower rectal temperature (T_{re}) response at rest in both a cool and hot environment while wearing normal military combat clothing, and then examined the influence of this response on tolerance to exercise in the heat while wearing protective clothing. Nine men performed four randomly ordered trials involving 2 h of rest at ambient temperatures of either 23 °C or 40 °C followed by exercise at an ambient temperature of 40 °C. The double-blind ingestion of placebo or melatonin occurred after 30 min of rest. The mean T_{re} during rest at 23 °C had decreased significantly from 36.8 (SD 0.1) °C to 36.7 (SD 0.2) °C at 90 min following the ingestion of the drug, whereas values during the placebo trial did not change. The lower T_{re} response during the melatonin trial remained during the first 50 min of exercise in the heat while wearing the protective clothing. Since the final mean T_{re} at the end of exercise also was significantly reduced for the melatonin [39.0 (SD 0.4) °C] compared with the placebo [mean 39.1 (SD 0.3) °C] trial, tolerance times approximated 95 min in both conditions. During rest at 40 °C, melatonin did not affect the mean T_{re} response which increased significantly during the last 90 min from 36.9 (SD 0.1) °C to 37.3 (SD 0.1) °C. This increase in T_{re} during the rest period prior to donning the protective clothing decreased tolerance time approximately 30 min compared with the trials that had involved rest at 23 °C. Total heat storage summated over the rest and exercise periods was not different among the trials at 15 kJ · kg^{-1}. It was concluded that the small decrease in T_{re} following the ingestion of 5 mg of melatonin at rest in a cool environment had no influence on subsequent tolerance during uncompensable heat stress.

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Introduction

Tolerance time while wearing nuclear, biological and chemical (NBC) protective clothing is a function of the initial core temperature, the rate of heat storage and the final core temperature tolerated at exhaustion. At a given metabolic rate, there is very little that can be done to alter the rate of heat storage when NBC clothing is worn unless microclimate conditioning can be used (McLellan et al. 1999a). Thus, those factors such as aerobic fitness (Cheung and McLellan 1998a) and heat acclimation (Aoyagi et al. 1995; McLellan and Aoyagi 1996) that lower the initial core temperature 0.2–0.3 °C increase tolerance time about 15% or 15–20 min during light exercise, whereas factors such as mild hypohydration (Cheung and McLellan 1998a, b) or the post-ovulatory phase of the menstrual cycle (Kolka and Stephenson 1997; Tenaglia et al. 1999) raise the starting core temperature and decrease tolerance time, again by about 15% during light exercise.

A fall in core temperature of 0.2–0.3 °C during bed-rest studies has been reported following the ingestion of 1–10 mg of melatonin (Cagnacci et al. 1992, 1994, 1996; Dawson et al. 1996; Deacon and Arendt 1995; Dollins et al. 1994; Reid et al. 1996; Strassman et al. 1991). Because of the influence of the initial core temperature on tolerance time while wearing NBC clothing, it was with interest that we examined this potential effect of melatonin ingestion on the decrease in rectal temperature (T_{re}) (McLellan et al. 1999b). An initial 1 mg dose was chosen to minimize the soporific side-effect of melatonin ingestion and supposedly at the same time optimize the decrease in T_{re} (Cagnacci et al. 1994; Dawson et al. 1996). However, we failed to observe any change in T_{re} during the 2 h following the ingestion of a 1 mg dose of melatonin at an ambient temperature of 23 °C prior to donning the NBC clothing, ingesting a second 1 mg

dose and exercising at an ambient temperature of 40 °C (McLellan et al. 1999b). We speculated that the orthostatic effects on T_{re} of changing from the seated to the standing position that have been demonstrated by Tikuisis and Ducharme (1998) during the dressing phase of the study may have negated the effect of the drug (Kräuchi et al. 1997). In addition, we attributed the minimal change in T_{re} to individual differences in sensitivity to the 1 mg dose of melatonin. We proposed that a higher dose of the drug might be necessary to observe a decrease in T_{re} during the non bed-rest conditions that we used to examine tolerance to uncompensable heat stress.

The purposes of the present study, therefore, were twofold: the first objective was to investigate the effects of a 5 mg dose of melatonin on thermoregulatory responses during rest at ambient temperatures of 23 °C and 40 °C while wearing normal military combat clothing, and, the second objective was to examine the effects of this 5 mg dose on subsequent tolerance time while wearing the NBC protective clothing during exercise at an ambient temperature of 40 °C. It was hypothesized that T_{re} during rest at 23 °C would be reduced following the ingestion of melatonin and that this decrease would prolong subsequent tolerance time while wearing the NBC clothing at 40 °C. It was also hypothesized that T_{re} would increase during the rest phase at 40 °C, independent of melatonin ingestion, and that this increase in temperature would decrease tolerance time in the NBC clothing compared with trials preceded by rest in the cooler 23 °C environment.

Methods

Subjects

Nine non heat-acclimatized men volunteered to participate in the study. The study was approved by the Institute's Ethics Committee, and complied with the current laws of Canada. Mean values for age, body mass, height, Dubois body surface area (A_D) and peakoxygen uptake ($\dot{V}O_{2peak}$), were 33.4 (SD 9.0) years, 79.51 (SD 11.4) kg, 1.78 (SD 0.06) m, 1.97 (SD 0.16) m^2 and 51.7 (SD 8.7) $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. All subjects were informed of all details of the experimental procedures and the associated risks and discomforts. After a medical examination to ensure that there were no medical contraindications to their participation in the experiment, each subject gave his written informed consent prior to the first day of data collection.

Experiment design

All subjects took part in four experiments in random order separated by a minimum of 7 and a maximum of 14 days. Most trials were performed weekly for a given subject. Subjects were asked to avoid hard exhausting exercise and the consumption of alcohol or nonsteroidal anti-inflammatory drugs (Murphy et al. 1996) for 24 h and caffeine for 12 h preceding each trial. All four trials began at approximately 0900 hours and consisted of 2 h of rest in ambient conditions of either 23 °C, 55% relative humidity or 40 °C, 30% relative humidity with low background lighting. The men wore underwear, jogging shorts, T-shirt, socks, lightweight cotton combat jacket and pants, and jogging shoes. Although this clothing would have reduced convective heat exchange compared with the wearing of shorts and a T-shirt, the combat clothing was selected for the rest periods since it would be the clothing worn by military personnel prior to donning the NBC overgarment. For each of the trials, this rest period was followed by walking on a level treadmill at 0.97 $m \cdot s^{-1}$ (3.5 $km \cdot h^{-1}$) in the environment chamber set at 40 °C and 30% relative humidity with a wind speed less than 0.1 $m \cdot s^{-1}$. In addition to the other clothing, subjects wore a semipermeable NBC overgarment, impermeable overboots and gloves, and a C4 respirator with canister. During the rest period at 40 °C, this additional clothing was warmed to the chamber temperature for 1 h prior to being donned for the exercise. The total thermal resistance of this clothing ensemble determined on a heated copper manikin was 0.29 $m^2 \cdot °C \cdot W^{-1}$ (1.88 clo) and the Woodcock vapor permeability coefficient determined using a completely wetted manikin was 0.33 (Gonzalez et al. 1993). After 30 min of rest, subjects ingested one capsule containing 5 mg of melatonin with metamucil (filler) or a placebo capsule (metamucil) administered in a double-blind manner. Exercise at 40 °C while wearing the NBC clothing continued until either rectal temperature (T_{re}) reached 39.3 °C, heart rate (f_c) remained at or above 95% of f_{cpeak} obtained during the determination of $\dot{V}O_{2peak}$ for 3 min, nausea or dizziness precluded further exercise, the subject asked to be removed from the chamber, or the investigator removed the subject from the chamber. Subjects also performed a familiarization trial, which included all aspects of the experimental trials, with the exception that no capsules were ingested, and used the same criteria for termination of the trial. This session was performed 7 days before the first experiment.

Dressing and weighing procedures

Subject preparation, insertion of the rectal thermistor, and placement of heat flux transducers and humidity sensors have been detailed previously (Aoyagi et al. 1994; McLellan et al. 1999b). Nude body mass was measured at the beginning and end of each trial, whereas dressed masses were recorded at the beginning and end of both the rest and exercise phases of each trial. The subject's humidity sensors, heat flux transducers and rectal thermistor were connected to a computerized data acquisition system (Hewlett-Packard 3497A control unit, 236–9000 computer and 2934A printer). Every minute average values for T_{re}, a 7-point weighted mean skin temperature ($\overline{T}_{sk}$) and mean heat flow ($\overline{HF}$) (Hardy and Dubois 1938), and unweighted average skin and garment vapor pressures were recorded and printed by the data acquisition system. The f_c was recorded every 5 min from the display on the telemetry receiver. Subjects were given 400 ml of warm water at approximately 37.0 °C to drink before to the 2 h rest at 40 °C. No water was consumed before the 2 h of rest at 23 °C. Subjects consumed 200 ml of warm water at the beginning and every 15 min during the treadmill walking. If T_{re} was above 39.0 °C or if the subject felt he could not continue much longer, water was no longer provided since masses obtained after the exposure might not have reflected the absorption of this fluid from the intestine.

Differences in nude body mass before and after each trial were adjusted for fluid intake and respiratory and metabolic loss of mass (see below). The sweat production rate during the exercise phase of each trial was calculated as the difference between the adjusted pre-trial and post-trial nude body masses, divided by tolerance time which was defined as the difference in time between the start and finish of walking in the environment chamber. It was not possible to obtain a nude body mass following the 2 h rest. However, differences in dressed mass were assumed to reflect fluid loss accurately and were used to adjust pre-trial nude body masses so values were representative of nude body masses prior to beginning the exercise phase of each trial.

Gas exchange analyses

Open-circuit spirometry was used to determine expired minute ventilation and oxygen consumption ($\dot{V}O_2$) for 2–3 min in every 15 min in each of the trials. During the rest period a Hans Ran-

dolph valve was used and for the walking phase an adapter was attached to the respirator which allowed expired gas to be collected. Respiratory water loss was calculated using the $\dot{V}O_2$ measured during the trial and the equation presented by Mitchell et al. (1972). Metabolic loss of mass was calculated from $\dot{V}O_2$ and the respiratory exchange ratio using the equation described by Snellen (1966).

Blood sampling

After the insertion of the rectal thermistor, a 20 gauge catheter (Vialon Insyte, Becton Dickinson) was inserted into an antecubital vein and a small-bore 20 in extension line was connected to the catheter and taped down the forearm to exit at the wrist. The line was kept patent using 10 IU $\cdot$ ml^{-1} of heparin. This system allowed blood sampling to occur when the subject was dressed in the NBC clothing. After insertion of the catheter the subjects stood for 15 min and then an initial 10 ml sample was taken. The initial blood sample was used to determine plasma melatonin concentration and serum osmolality calculated from sodium, glucose and urea nitrogen concentrations (Stat Profile Ultra, Nova Biomedical). Subsequent determinations of plasma melatonin concentrations were made from 5ml of blood drawn after 25 min of rest (just prior to capsule ingestion), after 115 min of rest and after 45 min of walking.

Blood flow measurements

During the 2 h rest, forearm blood flow was determined at 30, 60, 90, and 120 min using venous occlusion strain-gauge plethysmography (Hokanson, Bellevue, Wash.). Blood flow was determined using the catheter-free arm.

Determination of plasma melatonin concentration

Melatonin was analysed using a negative ion chemical ionization gas chromatograph mass spectometry/mass spectometry (GC-MS/MS) technique that has been described in detail by McLellan et al. (1999b).

Heat storage

The rate of heat storage ($\dot{S}$ in watts per metre squared) during both the rest and exercise periods was calculated from the heat balance equation:

$$\dot{S} = \dot{M} - \dot{W} \pm \left(\dot{C} + \dot{R} + \dot{K}\right) \pm \dot{C}_{resp} - \dot{E}_{resp} - \dot{E}_{sk} \quad (1)$$

where $\dot{M}$ is rate of metabolic heat production, $\dot{W}$ is rate of external work done, and $\dot{C}$, $\dot{R}$, $\dot{K}$, $\dot{C}_{resp}$, $\dot{E}_{resp}$, and $\dot{E}_{sk}$ are rates of skin heat losses or gains by convection, radiation, and conduction and respiratory convection, respiratory evaporation and skin evaporation, respectively.

The specific equations used to determine the different components of the heat balance equation have been described in detail previously (McLellan et al. 1999b).

Heat storage capacity, S in kilojoules per kilogram, was calculated from $\dot{S}$ and tolerance time as,

$$S = \dot{S} \cdot A_D \cdot \text{mass}^{-1} \cdot (60 \cdot \text{time}) \cdot 1{,}000^{-1} \quad (2)$$

Statistical analyses

Rest and exercise data were analysed separately. A two factor (drug and temperature) repeated measures ANOVA was used to evaluate any differences among the trials for osmolality, sweat production, average metabolic rate, heat storage and tolerance time. A three-factor (drug, temperature and time) repeated measures ANOVA was used to evaluate the changes in $\dot{V}O_2$, f_c, T_{re}, $\overline{T}_{sk}$ and $\overline{HF}$ during the exposures. When a significant F-ratio was obtained, a Newman-Keuls post-hoc analysis was used to isolate differences among treatment means. For all statistical analyses, the 0.05 level of significance was used.

Results

Indices of body hydration

There were no differences among the trials for either nude body mass or osmolality, thus indicating that body hydration was similar at the beginning of the trials. Since no fluid was provided during the 2 h of rest at 23.0 °C, dressed mass decreased significantly from a mean of 82.7 (SD 10.2) kg to 82.6 (SD 10.2) kg. In contrast, 400 ml of fluid was provided at the beginning of the 2 h of rest at 40.0 °C in an attempt to balance the greater expected fluid loss. Under this condition, there was a small but significant increase in mean dressed mass from 82.6 (SD 10.1) kg to 82.7 (SD 10.1) kg.

Plasma melatonin

Throughout the placebo trials, melatonin concentrations remained below 20 pg $\cdot$ ml^{-1}. In contrast, 90 min following the ingestion of the 5 mg dose of melatonin during rest, plasma concentrations increased significantly to approximately 5,000 pg $\cdot$ ml^{-1}. Values remained significantly elevated at approximately 4,000 pg $\cdot$ ml^{-1} after 45 min of exercise. The environmental temperature had no effect on plasma melatonin concentrations.

Indices of heat strain

Forearm blood flow

Melatonin ingestion did not affect forearm volume blood flow during the rest period. During rest at 23 °C, mean values did not change significantly from 4.3 (SD 1.0) ml blood $\cdot$ 100 ml tissue^{-1} at 30 min to 4.0 (SD 1.1) ml blood $\cdot$ 100 ml tissue^{-1} after 2 h. At 40 °C, blood flow increased significantly with time such that the value of 6.0 (SD 3.2) ml blood $\cdot$ 100 ml tissue^{-1} after 2 h of rest was greater than the flow of 4.2 (SD 1.6) ml blood $\cdot$ 100 ml tissue^{-1} recorded after 30 min.

Metabolic rate

The metabolic rate averaged over the 2 h rest period was not affected by melatonin ingestion or the temperature of the environment and approximated 50 W $\cdot$ m^{-2}. During exercise at 40 °C in the NBC clothing, the average metabolic rate also was not different among the trials and approximated 175 W $\cdot$ m^{-2}.

Rate of sweat production and evaporation

The rate of sweat production was not determined during the rest period since it was not possible to obtain a nude body mass at the end of the 2 h of rest. Undressing and then redressing the subjects with the heat flux transducers would have taken a further 45–60 min. Sweat rates were not different among the trials during the exercise in the NBC clothing at 40 °C (Table 2). The rate of sweat evaporation, calculated from the humidity sensor data and the model described by Cain and McLellan (1998), revealed no effect of melatonin ingestion either at rest or during exercise (Tables 1, 2). However, sweat evaporation was greater during the rest period at 40 °C.

Heart rate

Figure 1 presents the changes in f_c during the trials at rest and exercise. Values increased significantly with time while resting at 40 °C whereas a small but significant decline was noted during rest at 23 °C. During exercise at 40 °C while wearing the NBC clothing, f_c was higher throughout if preceded by rest at 40 °C. Melatonin ingestion had no effect on the f_c response either at rest or during exercise.

Rectal temperature

During rest at 23 °C, a small but significant decline in T_{re} was recorded 90 min following the ingestion of the 5 mg dose of melatonin (Fig. 2). This significant difference in T_{re} between the drug and placebo trials remained during the first 50 min of exercise at 40 °C while wearing the NBC clothing. After 70 min of exercise, there was no longer a significant main effect of the drug on the T_{re} response ($P < 0.07$). The mean T_{re} recorded at the end of the exercise and heat-stress following the ingestion of melatonin during rest at 23 °C was also significantly reduced (39.0 °C) compared with the placebo (39.1 °C) (Table 2). During the 2 h rest period at 40 °C, melatonin ingestion had no effect on the 0.5 °C increase in T_{re}. Melatonin also did not affect the T_{re} response during the subsequent exercise while wearing the NBC clothing nor did the drug influence the T_{re} tolerated at the time of exhaustion (Table 2). Differences in T_{re} during rest at 23 °C or 40 °C became progressively more evident during the last 90 min of rest and these differences remained during the exercise period. In addition, the time required for a 1.0 °C increase in T_{re} while wearing the NBC clothing was significantly longer when subjects were dressed at 23 °C in the protective ensemble prior to entering the environment chamber at 40 °C (Table 2). This finding could be attributed to the slower increase in

Table 1 Sweat evaporation, rate of heat storage and the amount of heat storage during the rest period at either 23 °C or 40 °C while wearing the combat clothing and ingesting either a melatonin or placebo capsule ($n = 8$)

	23 °C				40 °C			
	Melatonin		Placebo		Melatonin		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
*Sweat evaporation rate ($W \cdot m^{-2}$)	5.2	6.2	2.0	4.4	50.0	19.2	54.0	23.8
*Rate of heat storage ($W \cdot m^{-2}$)	−13.4	8.4	−9.5	4.0	22.2	19.1	20.0	23.0
*Heat storage ($kJ \cdot kg^{-1}$)	−2.4	1.5	−1.7	0.7	4.0	3.4	3.8	2.3

* Significant differences in melatonin and in placebo treatments between 23 °C and 40 °C

Table 2 The rates of sweat production and sweat evaporation, final skin and rectal temperatures, the time required for a 1.0 °C increase in rectal temperature, tolerance time, the rate of heat storage and the amount of heat storage for the exercise period at 40 °C and 30% relative humidity while wearing the nuclear, biological and chemical protective ensemble after the ingestion of a melatonin or placebo capsule during prior rest at either 23 °C or 40 °C. Values are for $n = 8$ unless otherwise stated

	Prior rest at 23 °C				Prior rest at 40 °C			
	Melatonin		Placebo		Melatonin		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sweat production rate ($kg \cdot h^{-1} \cdot m^{-2}$)	0.898	0.253	0.868	0.226	0.866	0.341	0.841	0.295
Sweat evaporation rate ($W \cdot m^{-2}$)	55.7	16.1	58.2	37.6	66.6	20.1	63.2	24.4
[a]Final skin temperature (°C)	38.1	0.3	38.1	0.3	38.3	0.4	38.3	0.4
Final rectal temperature (°C) ($n = 9$)	38.96[b]	0.37	39.07	0.30	38.99	0.32	39.05	0.33
[a]Time for 1.0 °C increase in rectal temperature (min) ($n = 9$)	51.4	9.0	50.8	5.9	44.7	8.6	43.9	8.9
[a]Tolerance time (min) ($n = 9$)	92.8	12.3	95.3	8.9	63.4	12.9	64.4	9.1
Rate of heat storage ($W \cdot m^{-2}$)	121.9	18.9	120.9	36.2	109.7	20.7	112.6	25.8
[a]Heat Storage ($kJ \cdot kg^{-1}$)	17.5	3.3	17.6	5.9	10.9	3.1	12.0	4.1

[a] Significant difference between prior rest at 23 °C or 40 °C
[b] Significantly different from placebo

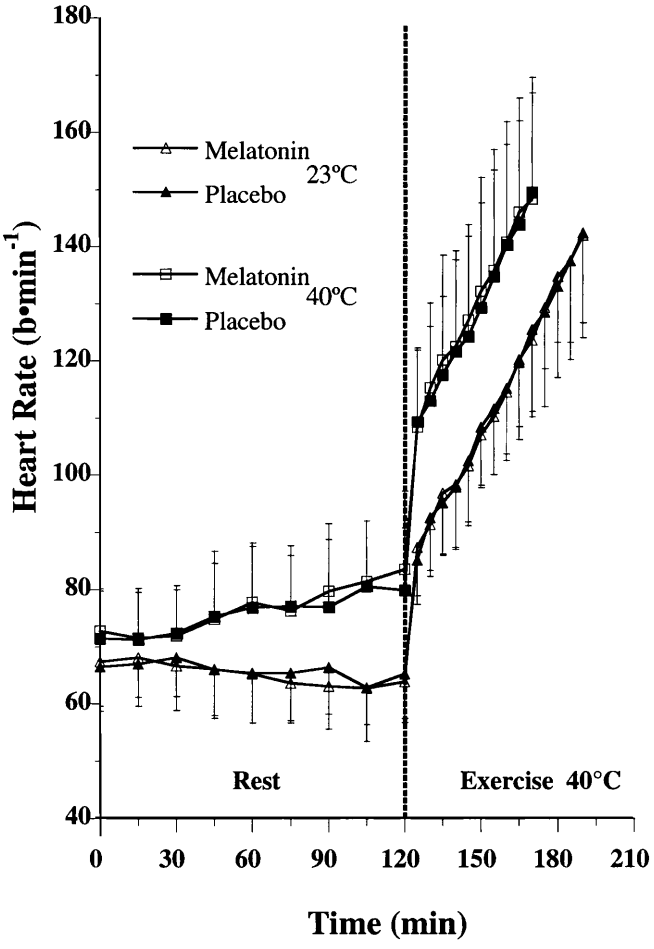

Fig. 1 Changes in heart rate during the 2 h rest at either 23 °C or 40 °C while wearing combat clothing and during subsequent exercise at 40 °C and 30% relative humidity while wearing the nuclear, biological and chemical protective ensemble. A 5 mg dose of melatonin or a placebo capsule was ingested after 30 min of rest. Values are mean and SD for $n = 9$

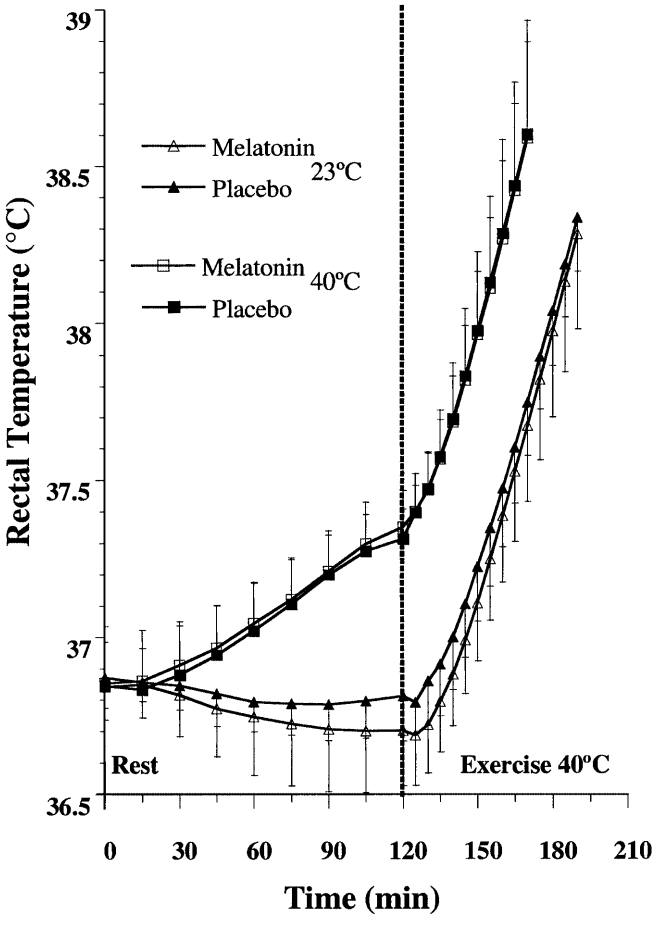

Fig. 2 Changes in rectal temperature during the 2 h rest period at either 23 °C or 40 °C while wearing combat clothing and during subsequent exercise at 40 °C and 30% relative humidity while wearing the nuclear, biological and chemical protective ensemble. A 5 mg dose of melatonin or a placebo capsule was ingested after 30 min of rest. Values are mean and SD for $n = 9$

T_{re} during the initial 15 min of exercise for trials that were preceded by rest at 23 °C. The rate of increase in T_{re} during the latter stages of exercise were very similar among all trials.

Mean skin temperature

Melatonin had no influence on the response of this dependant measure. However, $\overline{T}_{sk}$ was significantly higher throughout the trials that involved rest at 40 °C. Final $\overline{T}_{sk}$ also was significantly increased at the end of the exercise period if the rest had been at 40 °C rather than at 23 °C (Table 2).

Hand and mean heat flow

Melatonin had no influence on the heat flow from the hand during the rest period at either 23 °C or 40 °C. Mean values averaged over the 90 min period following the ingestion of the placebo or drug were 77.8 (SD 23.4) and 78.6 (SD 28.9) $W \cdot m^{-2}$, respectively, at 23 °C and −28.8 (SD 7.7) and 27.9 (SD 6.3) $W \cdot m^{-2}$, respectively, at 40 °C. Melatonin also had no affect on $\overline{HF}$ during the rest or exercise periods.

Heat storage

Neither the rate nor the amount of heat storage were affected by the ingestion of melatonin (Tables 1, 2). During rest at 23 °C, calorimetric estimates of heat storage indicated heat loss from the body whereas at 40 °C the calculations showed increases in body heat content (Table 1). During exercise at 40 °C while wearing the NBC clothing, the rate of heat storage was similar for all trials. However, the change in heat content of the body from the beginning of exercise was significantly reduced if the rest had occurred at 40 °C (Table 2). The total increase in heat content calculated

from the sum of the changes during the rest and exercise periods was similar among all conditions (Tables 1, 2) and approximated 15 kJ · kg^{-1}.

Heat tolerance

Tolerance time while wearing the NBC clothing was not affected by melatonin ingestion but was reduced by approximately 30 min following the 2 h rest at 40 °C compared with rest in the cooler environment of 23 °C (Table 2). For the 36 trials, exhaustion was stated as being the reason for ending the exposure in 10 tests, dizziness in 8 trials, nausea and breathing difficulty in 1 case each, and reaching a T_{re} of 39.3 °C in 16 tests.

Discussion

The results from the present study have revealed two main findings. First, a small decrease in T_{re} was observed following the ingestion of 5 mg of melatonin only during rest in a cool environment at 23 °C. This decrease in T_{re} had no influence on tolerance times during the subsequent heat stress of wearing NBC clothing at 40 °C. Second, melatonin ingestion had no influence on the rise in T_{re} during rest at 40 °C. This increase in T_{re} during the rest period subsequently reduced tolerance time in the NBC clothing compared with trials involving rest at 23 °C.

Decreases in T_{re} following the ingestion of 1–10 mg of melatonin have been well documented in humans (Cagnacci et al. 1992, 1994, 1996; Dawson et al. 1996; Deacon and Arendt 1995; Dollins et al. 1994; Reid et al. 1996; Strassman et al. 1991) and thus the decrease observed during the resting phase at 23 °C in the present study is consistent with these previous reports. However, the 0.1 °C fall in T_{re} during the current investigation was less than the 0.2–0.3 °C decrease reported by these other authors. Most (Cagnacci et al. 1992, 1994, 1996; Dawson et al. 1996; Dollins et al. 1994; Reid et al. 1996; Strassman et al. 1991), but not all (Deacon and Arendt 1995), of these other studies involved controlled supine or seated rest to eliminate the influence of activity, exposure to bright light and changing posture on core temperature. Light intensity was controlled between 500 and 700 lx in the present study. Also, in the present study, posture was controlled in the seated position for 30 min before and 90 min following the ingestion of the melatonin. Tikuisis and Ducharme (1998) have documented a 0.2 °C fall in T_{re} during a 2 h period in changing from the standing to the seated position and a further decrease of 0.3 °C in changing to the supine position. In addition, Kräuchi et al. (1997) have revealed that an orthostatic challenge in changing from the supine to the upright position negated the effect of a 5 mg dose of melatonin on the fall in T_{re}. Thus, although posture was controlled in the present study, the orthostatic challenge that remained while in the seated position may have been sufficient to negate the greater effect of melatonin on the decrease in T_{re} that has been observed during bed rest (Cagnacci et al. 1992, 1994, 1996; Dawson et al. 1996; Dollins et al. 1994; Reid et al. 1996; Strassman et al. 1991). Interestingly, none of these previous studies reported the clothing that was worn by their subjects. We cannot discount, therefore, that the combat clothing had a greater thermal resistance than the clothing worn by subjects in these other studies and that these differences in the properties of the clothing materials may have accounted for the smaller decrease in core temperature observed during the rest period at 23 °C in the present investigation.

The mechanism responsible for the decrease in T_{re} following melatonin ingestion remains unclear. Our calorimetric estimates of heat storage were not sensitive enough to detect the 0.1 °C decrease in T_{re} recorded following the ingestion of melatonin at 23 °C. Measurements of forearm blood flow, mean heat flow from the body, heat loss from the hand in particular, metabolic rate and estimates of evaporative heat loss failed to show any effect of the ingestion of the drug. In contrast, Kräuchi and Wirz Justice (1994) observed an increase in foot temperature that correlated in time with the fall in T_{re} following the ingestion of 5 mg of melatonin during bed rest. Van den Heuvel et al. (1999) also reported an increase in hand temperature following the intravenous injection of melatonin. These findings together with results from animal studies (Rozenboim et al. 1998) imply that melatonin increases peripheral cutaneous vasodilatation to promote an increased convective heat loss. This explanation is consistent with the following observations: first, an orthostatic challenge and the increase in vasoconstrictor tone in changing from the supine to the upright position negates the effect of a 5 mg dose of melatonin on the decrease in T_{re} (Kräuchi et al. 1997), and second, the vasodilatatory response observed during rest at 40 °C, as shown by the increase in forearm blood flow, was sufficient to negate any further vasodilatatory response due to melatonin ingestion. Also, during rest at 40 °C, melatonin had no effect on evaporative heat loss implying that melatonin did not influence the sudomotor response to heat stress.

We hypothesized that the 5 mg dose of melatonin would decrease T_{re} at rest at 23 °C and that this decrease would increase tolerance time during exercise when the protective clothing was worn at 40 °C. Although melatonin ingestion at rest was associated with a small but significant decrease in T_{re} that remained during the exercise and heat exposure while wearing the NBC clothing, there was also a small but significant reduction in the final T_{re} during this melatonin trial. Thus, tolerance time remained similar to the placebo condition. Therefore, our hypothesis must be rejected. Given that there was little, if any, evidence to support an ergogenic effect following the melatonin ingestion and that the drug also has soporific side-effects (Dollins et al. 1994; Reid et al.

1996), we do not feel it is worthwhile to perform additional studies during uncompensable heat stress that involve doses in excess of 5 mg.

Webb (1995) has proposed that the body regulates heat content, rather than core temperature. The findings from the present study together with our previous comparisons between morning and afternoon trials of uncompensable heat stress (McLellan et al. 1999b) support this theory of heat regulation. Indeed, there were no significant differences in total heat storage among the conditions in the current investigation when the changes in heat storage during the rest and exercise periods were summated (see Tables 1, 2). There are certain conditions, however, where a change in the core temperature at rest alters total heat storage when NBC clothing is worn. For example, factors such as aerobic fitness (Cheung and McLellan 1998b) and heat acclimation (Aoyagi et al. 1995; McLellan and Aoyagi 1996) which lower core temperature at rest are associated with an increased heat storage and tolerance time. Conversely, factors such as mild hypohydration (Cheung and McLellan 1998a, b) or the post-ovulatory phase of the menstrual cycle (Kolka and Stephenson 1997; Tenaglia et al. 1999), which raise resting core temperature, have the effect of lowering total heat storage and reducing tolerance time. In addition, Gonzalez-Alonso et al. (1999) recently reported that well-trained cyclists became fatigued at the same core temperature of approximately 40 °C during uncompensable heat stress regardless of changes to the initial core temperature or rates of heat storage. What accounts for the body's ability to alter heat storage under some conditions and not others is unclear at this time.

In summary, the present study has revealed that the ingestion of 5 mg of melatonin was associated with a small decrease in T_{re} during rest in a cool environment which remained during subsequent exercise in NBC clothing at 40 °C. However, the final core temperature during exercise also was reduced such that tolerance time was unaffected by the ingestion of the drug. The findings have also shown that the 0.5 °C increase in core temperature during a 2 h resting period at 40 °C was not affected by the ingestion of melatonin. This increase in T_{re}, at rest, however, reduced tolerance time when NBC clothing was worn by approximately 30% compared with trials which had been preceded by rest in a cool environment. Partitional calorimetric estimates of total heat storage showed a similar increase in body heat content prior to exhaustion regardless of drug ingestion or temperature of the resting environment.

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