Exertional fatigue, sleep loss, and negative energy balance increase susceptibility to hypothermia

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Young, Andrew J., John W. Castellani, Catherine O’Brien, Ronald L. Shippee, Peter Tikuisis, Lloyd G. Meyer, Laurie A. Blanchard, James E. Kain, Bruce S. Cadarette, and Michael N. Sawka. Exertional fatigue, sleep loss, and negative energy balance increase susceptibility to hypothermia. J. Appl. Physiol. 85(4): 1210–1217, 1998.—The purpose of this study was to determine how chronic exertional fatigue and sleep deprivation coupled with negative energy balance affect thermoregulation during cold exposure. Eight men wearing only shorts and socks sat quietly during 4-h cold air exposure (10°C) immediately after (~2 h, A) they completed 61 days of strenuous military training (energy expenditure ~4,150 kcal/day, energy intake ~3,300 kcal/day, sleep ~4 h/day) and again after short (48 h, SR) and long (109 days, LR) recovery. Body weight decreased 7.4 kg from before training to A, then increased 6.4 kg by SR, with an additional 6.4 kg increase by LR. Body fat averaged 12% during A and SR and increased to 21% during LR. Rectal temperature (Tre) was lower before and during cold air exposure for A than for SR and LR. T(Re) declined during cold exposure in A and SR but not LR. Mean weighted skin temperature (Tsk) during cold exposure was higher in A and SR than in LR. Metabolic rate increased during all cold exposures, but it was lower during A and LR than SR. The mean body temperature (0.67 Tsk + 0.33 Tsk) threshold for increasing metabolism was lower during A than SR and LR. Thus chronic exertional fatigue and sleep loss, combined with underfeeding, reduced tissue insulation and blunted metabolic heat production, which compromised maintenance of body temperature. A short period of rest, sleep, and refeeding restored the thermogenic response to cold, but thermal balance in the cold remained compromised until after several weeks of recovery when tissue insulation had been restored.

exhaustion; underfeeding; sleep deprivation; body temperature regulation

EACH YEAR, OVER 1,300 SOLDIERS UNDERTAKE AN ARDUOUS 9-WK TRAINING COURSE AT THE UNITED STATES ARMY RANGER SCHOOL. THROUGHOUT THE ENTIRE 9 WK, STUDENTS ENGAGE IN VERY STRENUGIOUS PHYSICAL ACTIVITY (15, 24) AND THEY ARE DELIBERATELY UNDERFED, SO THAT OVERALL ENERGY BALANCE IS SUFFICIENTLY NEGATIVE TO CAUSE SUBSTANTIAL BODY WEIGHT LOSS (15, 24). ALSO, STUDENTS AVERAGE ONLY ~4 H OF SLEEP EACH DAY (20). BECAUSE THIS OUTDOOR TRAINING IS CONDUCTED THROUGHOUT THE YEAR, STUDENTS OFTEN EXPERIENCE MODERATE-TO-SEVERE COLD STRESS CAUSED BY PROLONGED EXPOSURE TO COLD AIR, WIND, RAIN, AND WATER IMMERSION. INDEED, ON FEBRUARY 15, 1995, A CLASS OF STUDENTS TRAINING IN A SWAMP IN FLORIDA SUFFERED A NUMBER OF HYPOTHERMIA CASUALTIES, FOUR OF WHICH ULTIMATELY PROVED FATAL. SUBSEQUENTLY, THE QUESTION AROSE: IS SUSCEPTIBILITY TO HYPOTHERMIA INCREASED IN THESE RANGER SCHOOL STUDENTS BECAUSE OF PHYSIOLOGICAL CONSEQUENCES OF THEIR TRAINING?

The anecdotal association between exertional fatigue and susceptibility to hypothermia is well reported (21, 22), and a recently reported experimental study (26) suggests that prolonged fatiguing exercise can impair thermoregulatory responses to cold. Underfeeding and chronic negative energy balance may impair thermoregulatory responses to cold directly, by limiting substrate availability for thermogenesis and reducing body lean and fat mass (decreased insulation and thermogenic capacity), or indirectly, via central nervous or sympathoadrenal system effects (2, 9). Therefore, Ranger School students might indeed experience an increased susceptibility to hypothermia as they progress through the course.

This investigation examined whether physiological responses to cold were impaired in students immediately after they completed Ranger School and after subsequent recovery. In addition, the experiments were designed to identify possible physiological mechanisms by which fatigue and underfeeding may affect thermoregulatory responses to cold.

METHODS

Experimental design and subjects. Ideally, physiological responses to cold would have been measured in subjects immediately before they began Ranger School and again immediately after completing the school. However, attrition is high at the Ranger School; often ~50% of a given class graduates. Thus, even if an inordinately large number of subjects had undergone cold testing before beginning Ranger School, there would have been no way of ensuring that sufficient numbers of these students would complete the course and be available for a second trial. Furthermore, students do not arrive at Ranger School until just before training begins, after which their schedule precludes participation in experiments like those required for this study.

As an alternative approach, 15 men from a Ranger School class that was nearing completion of the training course were recruited as subjects for this research study, which had been approved by the appropriate Institutional Review Boards. The men volunteered to participate after being fully informed of the associated requirements and risks. The experimental design used was to measure physiological responses during three standardized cold exposure tests completed: 1) immediately (within 2 h) after the volunteers had completed the final field exercise of the Ranger training course (trial A); 2) after a short (48 h) rest and recovery period (trial SR); and 3) after a long (109 day) recovery period (trial LR). By assuming that
the long recovery period preceding trial LR was sufficient to restore physiological responses to levels found before Ranger School training, this design approach allowed us to infer the effects of Ranger training on responses to cold. The inclusion of trial SR offered the possibility of differentiating the effects of the multiple stressors such as exertional fatigue, sleep deprivation, hydration, and substrate depletion, from the chronic effects of prolonged negative energy balance. The only measure contained in this report that was obtained before the subjects began the training course is their initial body weight, which was extracted from Ranger School entrance medical examination records. Because of the student attrition during Ranger School, the pool of potential volunteers from which test subjects were recruited might be considered “survivors” of the stressors under investigation, e.g., fatigue and nutritional deprivation. Therefore, subject selection bias introduced by the experimental design used may theoretically limit the applicability of the findings from this study to other populations. However, the effects, if any, of such a bias are probably negligible, because many factors, including academic and motivational deficiencies, account for as much or more student attrition than do biomedical factors (physical fitness and injury).

On completion of the final field exercise of the course, and without being allowed to sleep or eat, the volunteers were transported (1 h) from the Florida Ranger Camp to the Naval Aerospace Medical Research Laboratory in Pensacola, FL. On arrival, the subjects completed a questionnaire that asked them to recall their sleep and food intake over the past day and to rate subjectively their sensation of fatigue by selecting one of following terms: extremely exhausted, somewhat exhausted, or OK. After the subjects’ anthropometric characteristics were assessed and subjects were dressed and instrumented, trial A commenced (~2 h after completion of Ranger training). After this trial, a 48-h recovery period ensued, during which food and fluid consumption and activity were ad libitum. The subjects then returned to the laboratory for trial SR. When trial SR was completed, subjects were released to return to their home bases. After 108 days of unsupervised recovery, 8 of the 15 subjects traveled to the United States Army Research Institute of Environmental Medicine in Natick, MA, where trial LR was completed according to the same protocol and at the same time of day as trials A and SR. Subjects abstained from alcohol for 24 h before each trial, and they refrained from consuming food or fluids except water for 8 h before each trial. Otherwise, food and fluid consumption and activity were ad libitum, and records were not maintained during the recovery periods.

All three experiments were conducted at the same time of day and according to the same protocol. After measurements were made of their height, nude weight, and skinfold thickness, the men dressed in cotton athletic shorts and socks. Sensors to measure electrocardiogram and body temperature (Tb) were connected, and a catheter was inserted into an antecubital vein to obtain blood samples. The subjects then sat quietly wrapped in blankets at normal room temperature (ambient air temperature 21–23°C) for ~1 h while they completed computerized cognitive and mood tests. Tb was then measured for 5 min. A venous blood sample was obtained, and resting metabolic rate was then measured. The subjects then arose and, leaving the blankets behind, walked into the climatic chamber (ambient air temperature set at 10°C) and sat quietly on a nylon webbed chair. Cold exposures lasted for 4 h, unless terminated earlier by the medical monitor (signs or symptoms of cold injury, or core temperature <35°C) or the volunteer chose to withdraw.

Experimental procedures. Tb and skin heat flow were measured every minute during cold exposure by using an automated system. Rectal temperature (Trect) was measured by using a thermistor inserted 10 cm beyond the anal sphincter. Skin temperature (Tsk) was measured by using a thermistor disk sensor (Concept Engineering, Old Saybrook, CT) attached on the skin surface at five sites (upper chest, triceps, forearm, thigh, and calf). Mean weighted skin temperature (Tskw) was calculated as 0.34 chest + 0.075 triceps + 0.075 forearm + 0.33 thigh + 0.18 calf Tsk (7). Mean Tc (Tb) was calculated as 0.67 Trect + 0.33 Tsk. Heart rate was measured every 5 min from the electrocardiogram obtained from three electrodes (CM-5 configuration) and radiotelemetered to an oscilloscope-cardiotachometer (Hewlett-Packard). Oxygen uptake, carbon dioxide output, and minute ventilation were measured by open-circuit spirometry at minutes 30, 60, 90, 150, and 210 of cold exposure. The oxygen and carbon dioxide pressures (Applied Electrochemistry 5-3A and Beckman LB-2, respectively) and volume (Tissot Spirometer) of a 2-min collection of the subjects’ air expired through a mouthpiece and hose into a 150-liter Douglas Bag were measured. Metabolic heat production was calculated from the calorific equivalent for the oxygen uptake at that respiratory exchange ratio. Immediately after each of the oxygen uptake measurements, subjects were asked to provide a rating of their perception of thermal sensation by using a numerical rating scale (30).

Blood samples were collected into ice-chilled tubes before and at the end of cold exposure. Samples were stored on ice until the cells were separated from the plasma by using a refrigerated centrifuge. Plasma glucose and lactate were measured immediately after separation of cells (model 2300, Yellow Springs Instruments, Yellow Springs, OH). The remaining plasma was frozen with the appropriate preservatives for later enzymatic assay of glycine (Sigma Diagnostics, St. Louis, MO), β-hydroxybutyrate acid (β-HBA, Sigma Diagnostics), and nonesterified free fatty acids (NEFA; Wako Chemicals, Osaka, Japan). In addition, norepinephrine was extracted from thawed plasma samples (ChromSystems, Munich, Germany), and the concentration was measured by using HPLC with electrochemical detection.

Data analysis. Although 15 subjects underwent testing during trials A and SR, only 8 of the 15 were available to complete trial LR. Therefore, except where specifically noted, only data from the eight subjects participating in all three trials were statistically analyzed and reported. Data were analyzed by using a computerized statistical software package (STATISTICA, Statsoft, Tulsa, OK). Data are reported as means ± SE. A two-factor (trial × cold-exposure duration) ANOVA for repeated measures was used to analyze the data. If significant main or interaction effects were indicated by ANOVA, then the Newman-Keuls procedure was used to determine significance of differences between pairs of observations. In addition, regression analysis was performed on each individual’s metabolic rate as a function of Tb and for rating of thermal sensation as a function of Tsk. ANOVA was then used to determine whether the slopes and intercepts of the regressions differed between trials. Unless otherwise indicated, significance of differences reported herein is P ≤ 0.05.

RESULTS

When they arrived at the laboratory for the first cold exposure (trial A), the subjects’ responses to the questionnaire documented that they were sleep deprived and underfed. They had averaged 1.5 h (range: 0–4 h) of sleep in the 24 h preceding this trial, and an average
of 22.5 h (range: 2–48 h) had elapsed since their most recent sleep period. Food intake during the previous 24 h averaged 300 kcal (range: 0–1,200 kcal), and the time since last food intake averaged 21.5 h (range: 3–48 h). Six men rated their feelings of fatigue as somewhat exhausted, whereas two reported feeling extremely exhausted.

Nutritional balance studies completed on 175 other men from the same class as the volunteers in these cold experiments indicated that, during the 9-wk Ranger School course, energy intake averaged ~3,300 kcal/day, and energy expenditure, estimated by adding this value to the caloric deficit calculated from the average changes in fat and lean mass, averaged ~4,100 kcal/day. Table 1 shows the body weight and fat content of the subjects who completed the cold experiments after completion of the School and again after 48 h and 16 wk of rest and recovery. Starting body weights, extracted from the subjects’ entrance physical examinations, are also shown. Body weights declined significantly during Ranger School, with an average loss of 7.4 kg at the end, when body fat content averaged ~12%. During the first 48 h of recovery, body weights increased, on average, 6.4 kg. Given the short duration of this recovery period, this weight gain was assumed to represent the acute effects of rehydration and food remaining in the gastrointestinal tract rather than true changes in lean and fat mass. After 16 wk of recovery, however, body weights had increased even more, averaging 12.8 kg more than when the course was completed. Body composition estimates from skinfold measurements indicated that this weight increase represented an increase in both lean and fat mass during this longer recovery period.

Subject attrition during each of the three cold exposures is shown in Fig. 1 as a function of exposure duration. The final Tr, measured before each subject ended exposure, did not differ among trials, averaging 35.97 ± 0.13, 36.05 ± 0.19, and 36.52 ± 0.10°C, for trials A, SR, and LR, respectively. Mean exposure duration was shortest (P < 0.05) during trial A (160 ± 18 min), significantly longer during trial SR (223 ± 13 min), and all subjects completed the entire 4-h exposure during trial LR. Ratings of thermal sensation provided during cold exposure are shown in Fig. 2. The ratings decreased (i.e., subjects felt colder) over the first 3 h of cold exposure, with no change thereafter. Lower ratings (colder) were provided during trial A (P < 0.05) than during trials SR and LR, during which ratings were similar to each other. When thermal sensations were examined as a function of Tsk, no significant differences among trials were found for the slope of the relationship, but the x-intercepts were higher during trial A than during trial SR (P < 0.07) and trial LR (P < 0.01), which did not differ from each other.

Table 1. Body composition changes after Ranger School training and with subsequent recovery

<table>
<thead>
<tr>
<th>Body Composition</th>
<th>Before Ranger School</th>
<th>Trial A</th>
<th>Trial SR</th>
<th>Trial LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass, kg</td>
<td>74.6 ± 2.9</td>
<td>67.2 ± 2.0</td>
<td>73.6 ± 1.7</td>
<td>80.0 ± 2.0</td>
</tr>
<tr>
<td>Fat, %</td>
<td>NA</td>
<td>11.6 ± 1.0</td>
<td>21 ± 1.0</td>
<td>*</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>NA</td>
<td>1.48 ± 0.27</td>
<td>4.98 ± 0.48</td>
<td>*</td>
</tr>
</tbody>
</table>

Values represent means ± SE; n, 8 men. Trial A was conducted 2 h after completion of Ranger School training. Trials SR and LR were conducted, respectively, after 48 h and 16 wk of recovery from Ranger School training. NA, data not available; *data unmeasured and assumed unchanged from trial A.
During trial LR, resting $T_r$ was significantly elevated compared with the other two trials. There was a significant decline in $T_r$, apparent after 60 min of cold exposure in both trials A and SR but not in trial LR. During trial LR, in fact, $T_r$ increased significantly by minute 30 of cold exposure, and this elevation persisted until minute 60, after which $T_r$ returned to preexposure values, where it remained constant until the end of the exposure. Throughout trial A, $T_r$ was significantly lower than at corresponding times during trials SR and LR. Differences in preexposure $T_r$ between trials SR and LR were eliminated by minute 30 of cold exposure, and, from minute 90 to the end of exposure, $T_r$ was significantly lower during trial SR than during trial LR. The $T_g$ before cold exposure was 1.4 and 1.3°C higher ($P < 0.05$) during trial SR than during trials A and LR, respectively, when there were no differences. $T_g$ fell lower ($P < 0.05$) during cold exposure in trial LR than during trials A and SR.

Metabolic heat production ($M$) before and during each of the three cold exposures is shown in Fig. 4. $M$ increased significantly during all three cold exposures. However, $M$ was significantly higher during trial SR than during trials A and LR, between which there was no difference. Figure 5 shows the regression describing $M$ (normalized for lean body mass) as a function of $T_g$ during each of the three trials. Although the slopes of the three regressions did not differ significantly, the $x$-axis intercept of the regression was less ($P = 0.06$) for trial A than for trials SR and LR. Similarly, the intercept, but not the slope, of the regressions calculated by using $M$ normalized for body surface area (data not shown) rather than lean body mass was lower ($P < 0.05$) for trial A than for the other trials.

The condition of the subjects, especially during trial A, made it extremely difficult to draw sufficient blood volume for the analyses planned. A complete set of blood samples before and after all three cold exposures was obtained from only three of the eight subjects participating in all three trials. The amount of missing data limited the utility of performing statistical analyses. Thus, for plasma glucose, lactate, NEFA, glycerol, and $\beta$-HBA concentrations, only means $\pm$ SE were computed, as shown in Table 2 along with the number of subjects from whom data were available. Plasma glucose concentrations appeared slightly lower, whereas NEFA and $\beta$-HBA appeared higher, before cold exposure during trial A than during the other trials. Plasma metabolite changes measured in seven additional subjects who did not complete trial LR (but from whom a complete set of blood samples was available for trials A and SR) followed the same pattern (data not shown). Preexposure metabolite values for all 11 subjects for
The primary finding from these experiments was that chronic exertional fatigue, sleep loss, and negative energy balance reduce cold tolerance and impair an individual’s ability to maintain normal Tb during cold exposure. This is demonstrated by the fact that the subjects’ core temperature fell during both cold-exposure tests performed shortly after completing Ranger School. In contrast, the subjects’ core temperature did not fall during the cold-exposure test performed after 16 wk of recovery after Ranger School. Several factors appear to act together to degrade the capability to defend thermal balance in chronically fatigued and underfed persons exposed to cold.

Weight loss because of chronic negative energy balance is an obvious factor that contributes to the subjects’ inability to maintain thermal balance during cold exposure after Ranger School. Initial body composition was not assessed, but others have documented losses of both fat and fat-free mass during this training (16, 24). In this study, there were increases in both fat and fat-free mass (9 and 3.8 kg, respectively) during the 16-wk recovery. Fat increases during recovery probably overestimate fat losses during preceding periods of negative energy balance, whereas increases in fat-free mass probably do provide a reasonable estimate of

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Trial A Before</th>
<th>Trial A After</th>
<th>Trial SR Before</th>
<th>Trial SR After</th>
<th>Trial LR Before</th>
<th>Trial LR After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mM</td>
<td>4.41 ± 0.21</td>
<td>5.19 ± 0.29</td>
<td>5.05 ± 0.14</td>
<td>4.92 ± 0.14</td>
<td>5.13 ± 0.14</td>
<td>5.31 ± 0.18</td>
</tr>
<tr>
<td>Lactate, mM</td>
<td>1.74 ± 0.30</td>
<td>2.02 ± 0.25</td>
<td>1.87 ± 0.12</td>
<td>2.45 ± 0.42</td>
<td>1.35 ± 0.11</td>
<td>1.62 ± 0.20</td>
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<tr>
<td>NEFA, mM</td>
<td>0.91 ± 0.29</td>
<td>1.16 ± 0.13</td>
<td>0.22 ± 0.04</td>
<td>0.28 ± 0.04</td>
<td>0.44 ± 0.08</td>
<td>0.48 ± 0.05</td>
</tr>
<tr>
<td>Glycerol, mM</td>
<td>0.06 ± 0.02</td>
<td>0.08 ± 0.03</td>
<td>0.06 ± 0.02</td>
<td>0.11 ± 0.03</td>
<td>0.03 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>β-HBA, mM</td>
<td>0.43 ± 0.06</td>
<td>0.40 ± 0.02</td>
<td>0.25 ± 0.04</td>
<td>0.25 ± 0.04</td>
<td>0.24 ± 0.04</td>
<td>0.16 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects whose data were included in average for each condition. Although n is the same before and after cold exposure in both trials A and SR, different subjects comprise the sample. Trial A was 2 h after completion of Ranger School training. Trials SR and LR were, respectively, after 48 h and 16 wk of recovery from Ranger School training. NEFA, nonesterified fatty acid; β-HBA, β-hydroxybutyric acid.
losses of lean tissue (3, 16). It seems safe to conclude that the 10% body weight loss that the subjects experienced over the 9 wk included both fat and muscle tissue.

Theoretically, loss of metabolically active lean body mass could limit the magnitude of shivering thermogenesis during cold exposure, but this does not seem to be the major consequence of the body weight loss. Metabolic heat production during cold exposure was the same in the third trial as in the first trial immediately after Ranger School, despite the gain of almost 4 kg fat-free mass after 16 wk of recovery. The more important consequence of the weight loss appears to be a decreased insulation against conductive heat loss from the body core to shell surface. Both fat and muscle contribute to the total body tissue insulation (27). This probably explains why $T_{sk}$ remained higher during the first two cold exposures compared with $T_{sk}$ during the third cold exposure completed 16 wk later, when subcutaneous fat thickness had more than tripled.

Decreased tissue insulation is not the only reason for the inability to maintain thermal balance in the cold after 9 wk of heavy exertion, sleep deprivation, and caloric deprivation. The short, 48-h recovery period partially ameliorated the thermoregulatory impairment apparent during the first trial. Although core temperatures declined during the second cold exposure after short recovery, temperatures remained higher than during the exposure immediately after the School, and six subjects completed the full 4-h exposure during the second trial compared with only one subject during the first trial. However, these between-trial differences do not reflect differences in physical insulation. Although body weights increased substantially between the first and second trials, this increase reflects the tremendous quantity of food and drink the subjects consumed during the short recovery period, because 48 h is insufficient time for tissue mass to significantly increase.

At least two factors may be acting together to help maintain higher core temperatures during the second cold exposure after the short recovery period. First, during the second trial, core temperatures were elevated even before cold exposure began. Thus, because of the higher initial (preexposure) level, core temperature did not fall as low over the course of the cold exposure as it did during the first trial. Secondly, metabolic heat production was higher during the second trial, after 48 h of recovery, compared with during the other two trials. The increased metabolic heat production during this trial was apparent before as well as during cold exposure, and this is very likely the reason that preexposure core temperatures were elevated.

Resting metabolic rate declines during chronic negative energy balance, in part because metabolically active tissue is lost, but also because the metabolic rate in the remaining tissue declines (28). Thus, rather than considering differences in metabolic heat production between the first two trials to indicate elevated metabolism during the second trial after the short recovery period, it would be more correct to view the difference as reflecting a suppression of metabolism during the first trial completed immediately after completion of Ranger School. This view is supported by the lower intercept for the regression of metabolic heat production as a function of $T_{b}$ during trial A compared with the intercepts for the relationships during trials SR and LR, which did not differ significantly from each other (see Fig. 5). Although metabolism increased with declining $T_{b}$ during all trials, the absolute rate of metabolic heat production at a given $T_{b}$ was reduced in these fatigued, nutritionally deprived men, and 48 h of rest and refeeding alleviated that suppression.

The mechanism for the suppression of metabolic heat production during cold exposure immediately after Ranger School remains unclear. Caloric deprivation from underfeeding might constrain metabolism by limiting energy substrate availability, i.e., a direct effect on peripheral thermogenic tissue. However, underfeeding by itself (without exertion) has had somewhat equivocal effects on metabolic responses to cold. Seven days of caloric restriction comparable to that experienced by the subjects in the present study reportedly had no effect on metabolic response during 40-min cold exposure (13). Forty-eight hours of starvation blunted women's thermogenic response to cold (13), but another study that used a similar protocol found that 48 h of starvation had no effect on men's metabolic response during 40 min of cold exposure (12). Hypoglycemia blunts cold-induced thermogenesis (6, 19), but the subjects in the present study were not hypoglycemic. On the other hand, the men's skeletal muscle glycogen stores were probably fairly low at the completion of Ranger School, because Jacobs et al. (8) demonstrated development of a substantial muscle glycogen depletion after as few as 4 days of military field maneuvers. However, depletion of skeletal muscle glycogen stores to low levels has no effect on metabolic heat production during cold exposures lasting >30 min (14, 31). Therefore, caloric deprivation per se is unlikely to account for the suppression of the thermogenic response to cold observed in the first trial.

The sustained high energy expenditure levels, the other component of the negative energy balance, may cause the suppression of the thermogenic response to cold. The high levels of energy expenditure sustained by the subjects in this investigation over many days led to a state of chronic fatigue that was exacerbated by sleep deprivation. Consistent with previous studies of Ranger School students (20), all subjects in this study reported feeling some degree of exhaustion and sleep deprivation during the trial immediately after Ranger School. Opstad (17) observed elevated basal levels of circulating norepinephrine in Norwegian Army Ranger students after 5 days of continuous military maneuvers involving sustained strenuous exertion, sleep deprivation, and extreme caloric restriction. Opstad (17) speculated that the chronic elevation in circulating norepinephrine had led to a peripheral adrenergic desensitization because the heart rate and blood pressure responses to further elevations in norepinephrine levels, induced by exercise, were blunted. If the rise in
norepinephrine exhibited by humans during cold exposure mediates or modulates the thermogenic response to cold, then peripheral adrenergic desensitization may also explain the suppression of the metabolic response to cold after the subjects of the present investigation completed their military training period.

In agreement with Opstad (17), we found in the present study that resting circulating norepinephrine levels were also observed elevated in the subjects immediately after the training course (see Fig. 6). Norepinephrine levels increased during all three cold exposures, and there did not appear to be much difference among trials in the response to cold. Sympathetic nervous stimulation mediates the nonshivering thermogenic response to cold in many animals (11), and it can produce a thermogenic response in humans (1). However, the importance of the norepinephrine response to cold in mediation of shivering thermogenesis in humans remains to be clearly demonstrated. Nevertheless, this mechanism bears further investigation, because it could explain the suppressed metabolic response to cold in the exhausted soldiers during the first trial.

As mentioned, the intercept for the regression of metabolic rate as a function of $T_b$ was lower when the soldiers were studied in the exhausted state than was observed after recovery for 48 h and 16 wk, but no significant differences were found among the regression slopes. This observation is consistent with a reduction in the set point for shivering thermogenesis while sensitivity of the response to the stimulus remained unchanged. That is, the onset of thermogenesis was delayed until $T_b$ reached a lower level when the subjects were exhausted compared with when they had recovered, but a similar increment in metabolic heat production was elicited for a given change in $T_b$ during all three trials. Opstad and Bahr (18) observed that, after short military maneuver periods (3–4 days) that involved intense exertion, negative energy balance, and sleep deprivation, the soldiers’ resting core temperatures declined, whereas resting metabolic rate increased (18). They speculated that this reflected a set point shift, but their rationale for that conclusion was not readily apparent. Recently, Savoure and Bittel (23) reported that, although resting core temperature was unaffected after 24 h of sleep deprivation, the onset of shivering during cold exposure was hastened; that is, shivering occurred at a higher $T_b$ than it did before sleep deprivation. In contrast, after longer periods of sleep deprivation (>33 h), resting core temperatures were found to be lower, and core temperature set points for thermoregulatory effector responses to heat stress were delayed, or shifted upward, even in the absence of negative energy balance and exertional fatigue (10). Such set point shifts during sleep deprivation may, in fact, represent phase shifting (advances or delays) of the circadian timekeeping for the rhythm of core temperature (25). Therefore, sleep deprivation, perhaps exacerbated by exertional fatigue, may have suppressed the exhausted subjects’ metabolic responses to cold during the first trial, and that suppression was quickly alleviated by rest and sleep during the 48-h recovery period.

Interestingly, the subjects reported feeling colder during cold exposure when they were exhausted compared with after recovery. Skin temperatures are generally thought to serve as the primary signal for thermal comfort sensations (4, 5). During the first cold-exposure trial, $T_{sk}$ were higher than during the third trial, and the same as during the second trial, yet thermal sensations were lower. Furthermore, the x-intercept for the relationship between thermal sensation and $T_{sk}$ was highest during the first trial, indicating that lower (colder) sensations were reported for a given $T_{sk}$ in the first compared with the other two trials. Core temperatures were lowest during the first trial. Therefore, core temperature may provide more input to the sensation of thermal comfort than was previously thought.

In summary, prolonged periods of sustained high levels of exertion and energy expenditure, coupled with negative energy balance and sleep deprivation, increase susceptibility to hypothermia. Thermogenic responses to cold are suppressed, probably because of fatigue that results from sleep deprivation and physical exertion. Negative energy balance causes loss of insulating body fat and thereby facilitates conductive heat loss during cold exposure. Recovery from the former can occur with a short period (48 h) of rest and sleep, but the latter requires a longer period of several weeks for refueling to restore body fat and insulation to normal levels.

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