Impaired thermoregulation and thyroid function in iron-deficiency anemia

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ABSTRACT  Ten women with iron-deficiency anemia, 8 with depleted iron stores (nonanemic), and 12 control women, all of similar body fatness, were exposed to a 28 °C water bath to test the hypothesis that iron-deficiency anemia impairs thermoregulatory performance. The anemic women had lower rectal temperatures than did control women (36.0 ± 0.2 vs 36.2 ± 0.1 °C, respectively, \( P = 0.001 \)) and a lower rate of oxygen consumption (5.28 ± 0.26 vs 5.99 ± 0.29 mL·min\(^{-1}\)·kg body wt\(^{-1}\), respectively, \( P = 0.04 \)) at 100 min of cold exposure. Plasma thyroxine and triiodothyronine concentrations were significantly (\( P < 0.002 \)) lower in anemic than in control women at baseline and during cold exposure. Responses of iron-depleted subjects were similar to those of control subjects. Iron supplementation corrected the anemia, significantly (\( P = 0.03 \)) improved rectal temperature at 100 min, and partially normalized plasma thyroid hormone concentrations. Plasma catecholamines were unaffected by iron status. This experiment demonstrates a functional consequence of iron-deficiency anemia in the balance of heat production and loss and suggests that thyroid-hormone metabolism may be responsible.  

KEY WORDS  Iron deficiency, temperature regulation, human subjects, plasma catecholamines, thyroxine, triiodothyronine

Introduction

Iron deficiency continues to be a significant nutritional-deficiency disease in many parts of the world. According to estimates by the World Health Organization, ~15% of the world's population has significant iron-deficiency anemia (1). In the United States, prevalence estimates from the second National Health and Nutrition Examination Survey (NHANES II) indicated that 1–6% of the population has impaired iron status (2). Numerous metabolic consequences of iron deficiency have been described (3–7). In the rat model, poor thermoregulation is one of these deleterious consequences (8–11), with indications that thyroid-hormone metabolism and catecholamine metabolism are both significantly altered in iron deficiency (8–13).

One preliminary report in humans (14) showed that iron-deficient-anemic subjects failed to thermoregulate normally during cold-water immersion, with a resultant significant loss of body temperature. Interpretation of that study was confounded by significantly lower body fat, as indicated by height-to-weight ratio, in iron-deficient-anemic compared with control subjects. Thus, the significantly greater metabolic rates and higher plasma norepinephrine concentrations in the anemic subjects could have been causally related to both their body fatness and their iron deficiency.

As an extension of our interest in alterations in thermoregulation during cold exposure in iron deficiency, we were prompted to use cold stress as a useful probe to examine how control of energy metabolism is perturbed in iron deficiency and, more specifically, how the hormones that control heat production and metabolic rates are affected by this single nutrient deficiency. We thus chose to examine thermoregulatory performance in young women with iron-deficiency anemia during a moderate cool-water immersion and to determine if alterations in thyroid hormone and catecholamine metabolism might be the underlying metabolic defects once the body fatness of subjects was strictly controlled. Moreover, we proposed to see if these alterations were repaired and reversed with oral iron supplementation.

Methods

Research design

This research was designed as a combined cross-sectional and longitudinal study using a pre- and posttreatment experimental design with oral iron supplementation as the treatment. Such a design allowed us to examine differences in thermoregulatory capacity between iron-deficient anemic (IDA), iron-depleted (IDP), and iron-sufficient control (C) women of similar percent body fat (cross-sectional comparison) and in IDA and IDP women before and after oral iron supplementation (longitudinal comparison). During the presupplementation phase of the study, thermogenic performance was assessed while each subject underwent two or three cool-water-bath exposures. Multiple cool-water exposures were performed on each subject because of intraindividual variation in certain physiological responses. After the initial exposures, the IDA and IDP women

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received 12 wk of oral iron supplementation (78 mg Fe/d as ferrous sulfate), and the control women received no supplementation. After the supplementation period, two to three cool-water-bath exposures were repeated in all three groups of subjects to determine the impact of oral iron supplementation on thermogenic performance in the IDA and IDP women.

Subject selection

Women were recruited for this study from The Pennsylvania State University campus through the use of announcements in academic classes, ads in the school newspaper, and flyers posted around the campus. Potential subjects reported for an initial screening, at which time the study protocol was fully explained, informed consent forms were signed, and a finger-prick blood sample was taken to assess the individual’s iron status from hemoglobin (Hb) and serum ferritin (SF) concentrations. Women were selected for participation in the study according to four criteria: 1) aged between 18 and 44 y; 2) free of any known metabolic disorders such as diabetes, hypoglycemia, or thyroid gland disorders as reported by the subject; 3) percent body fat between 20% and 30% as determined by hydrostatic weighing, including a nitrogen wash-out technique to estimate residual lung volume (15); and 4) iron status, with subjects classified as iron-deficient-anemic (Hb < 120 g/L and SF < 12 µg/L), iron-depleted (Hb > 120 g/L and SF < 12 µg/L), or iron-sufficient control (Hb > 120 g/L and SF > 20 µg/L). On the basis of these criteria, 10 IDA, 8 IDP, and 12 C women having a similar normal percent body fat were selected for the study. All subjects underwent a complete medical examination (medical history, electrocardiogram, blood pressure, and physical exam) by a physician before their participation in the study. The protocol for this study was approved by the Office for the Protection of Human Subjects at The Pennsylvania State University.

Water-bath data collection

On the day of the cool-water-bath exposure, subjects reported to the Noll Laboratory for Human Performance Research on the Penn State campus. The subject’s weight, time of last meal, and day of the menstrual cycle were recorded. Subjects fasted ≥ 5 h before the water bath to avoid the contribution of dietary thermogenesis to metabolic-rate measurements. In addition, the water-bath treatments were performed during the follicular phase (first 14 d) of the menstrual cycle to avoid the confounding effect of the increase in body temperature and metabolic rate that occurs during the luteal phase (last 14 d) of the cycle (16).

A nurse placed a 20-gauge catheter (Abbocath, Abbott Laboratories, Chicago) in the antecubital vein of the subject’s right arm to allow for periodic blood sampling during the water bath. After placement of the catheter, the subject entered a large water tank in a chair so that the water level was covering her shoulders. The subject’s right arm was placed on an armrest out of the water to prevent water from contacting the site of the catheter placement. The rectal thermistor was connected to a thermometer (Yellow Springs Instruments, Yellow Springs, OH) to measure core body temperature (±0.1 °C). A face mask (Respironics, Inc, Monroeville, PA) was placed over the subject’s nose and mouth to allow for the continuous collection of expired respiratory gases for oxygen consumption and metabolic-rate measurements. After the face mask was in place, the lights were turned down and the subject was instructed to relax in the warm water. This warm-water baseline period lasted for either 30 or 45 min, depending on how long it took the subject’s respiratory-gas measurements to stabilize at a baseline level. At the end of the baseline period, the nurse withdrew a 10-mL blood sample for later hematological and hormonal analyses, and core body temperature and respiratory-gas measurements were recorded.

At the end of the warm-water baseline period, 5 °C cool water and ice were added to the tank to mix with and replace the warm water and to quickly (10–15 min) lower the temperature of the water bath to 28 °C. A pump system circulated the cool water throughout the tank to ensure a uniform water temperature. The subject remained in this cool water for 100 min. At the time the water reached 28 °C (time 0) and at 20-min intervals thereafter until 100 min, a blood sample was drawn and core body temperature and respiratory-gas measurements were recorded. Figure 1 presents a timeline overview of the water-bath data-collection procedure. To facilitate the subject’s ability to remain in the cool water for 100 min, she was shown a movie on a videocassette recorder.

Blood analyses

Each subject’s iron status was assessed from Hb and SF concentrations from a capillary blood sample (17) during the screening procedure and from a venous blood sample during the cool-water-bath exposure. Hb and SF concentrations were measured colorimetrically by use of a cyanmethemoglobin method (Sigma Chemical Company, St Louis) and an enzyme-linked immunosorbent assay (ELISA) technique (18), respectively.

The 10-mL venous blood samples drawn at 20-min intervals during the cool water bath were equally partitioned into heparinized tubes for later hematologic and hormone analyses and into tubes containing EGTA and glutathione (Amersham Corp, Chicago) for catecholamine determination. The blood-collection tubes were kept on ice until they were centrifuged at 1350 × g for 12 min to separate the plasma from the red blood cells. The plasma was then frozen for later analysis of triiodothyronine (T3), thyroxine (T4), estrogen, progesterone, thyroid-stimulating hormone (TSH), epinephrine, and norepinephrine. Plasma samples were stored at −20 °C until later analysis except for the catecholamine samples, which were stored at −80 °C. Plasma T3, T4, and TSH as well as estrogen and progesterone were measured by radioimmunoassay (kits from Monobind, Costa Mesa, CA, and Serono Diagnostics, Inc, Norwell, MA, respectively). The coefficient of variation in all assays was < 6%. Plasma catecholamine samples were extracted and epi-
nephrine and norepinephrine concentrations were determined by use of high-pressure liquid chromatography with electrochemical detection (HPLC-EC) according to described methods (19). A refrigerated autosampler (Waters 712 WISP, Milli-pore Corp, Milford, MA) injected the samples, and an integrator (RC-3-a, Shimadzu Corp, Tokyo) was used to determine peak areas under the curve. Plasma epinephrine and norepinephrine concentrations were calculated based on a five-point standard curve and were corrected for recovery of the internal standard, dihydroxybenzylamine. The average recovery of the internal standard was 67%.

Respiratory-gas measurements

Continuous respiratory-gas measurements were made during the cool water bath by use of open-circuit methods. As described earlier, subjects wore a face mask (Respironics, Inc), which covered their nose and mouth. Sufficient continuous air flow was maintained through the mask to prevent the accumulation of carbon dioxide in the mask, and the flow rate was recorded. Oxygen and carbon dioxide concentrations of expired air were measured with an oxygen analyzer (Applied Electrochemistry S3-A, Sunnyvale, CA) and an infrared carbon dioxide analyzer (LB-2, Beckman, Fullerton, CA), respectively. A dual-channel chart recorder provided a continuous record of the oxygen and carbon dioxide concentrations of the subject’s expired air. The respiratory quotient (RQ), expired air volume/min (VE), and rates of oxygen consumption (VO2) and carbon dioxide production (VCO2) were calculated for the baseline period and the 20-min time points during the water bath by use of standard equations (20). Planimetry was used to measure the area under the oxygen curve, and the total volume (L) of oxygen consumed by the subject during the 100 min of cool-water-bath exposure was calculated.

For the determination of energy expenditure during the cool-water-bath exposure, we measured urinary nitrogen excretion in a post-water-bath urine sample in a subset of the subjects and calculated energy expenditure according to Weir’s equation (21). In addition, since the contribution of protein metabolism to overall energy metabolism is generally small (20), we calculated energy expenditure assuming that the RQ was representative of a nonprotein RQ. We found that energy expenditure during the cool water exposure as estimated by assuming a nonprotein RQ without correction for the contribution of protein metabolism varied from that estimated from a true nonprotein RQ (correction for urinary nitrogen excretion) by only 0–2% (data not shown). Thus, we elected to calculate each subject’s energy expenditure in kilocalories during the water bath by multiplying the thermal equivalent of oxygen (kilocalories expended per liter of oxygen consumed) (22), based on the subject’s nonprotein RQ value (average of RQ values at the 20-min time points), by the total liters of oxygen consumed during the bath, as determined from planimetry.

Statistical analyses

The general analytic scheme was a two-way repeated-measures analysis of variance (ANOVA) with iron group as the between-subject factor and supplementation status as the within-subject factor. There were two to three replicate water baths for each subject at both pre- and postsupplementation. We decided a priori to perform separate, cross-sectional analyses at the following three time points: baseline and 40 and 100 min of cool-water exposure. The significance of differences between means was determined by contrasts of the least-square means (LS means) for a priori comparisons of iron group by supplementation status. The level of significance used for each a priori test was P = 0.05.

We performed separate ANOVAs for each of the response measures. Before the analysis, we inspected the distribution of each response measure for possible departures from the standard ANOVA assumptions of normally distributed errors with constant variance. This inspection led us to make the following transformations: 1) the logarithm of plasma epinephrine was used as the dependent response in order to stabilize the error variance and 2) the median of the two or three replicates at each time sample was used as the dependent variable for plasma T4, T3, and TSH and for VO2 (mL•min−1•kg body wt−1) in order to decrease the influence of outlying data values. This latter analysis was then weighted by the number of replicates contributing to each median. The distribution of the remaining response variables conformed satisfactorily to ANOVA assumptions and did not require transformation.

Body composition data were analyzed by one-way ANOVA. All data presented in the figures are x± SEM. The hematologic and body composition data are presented as x± SD. All statistical analyses were performed by use of the Statistical Analysis System (SAS Institute Inc, Cary, NC).

Results

Our selection criteria based on SF and Hb concentrations and body fatness resulted in three groups of subjects (IDA, IDP, and C) that differed initially only in iron nutriture (Table 1). Both iron-deficient groups had depleted iron stores, as indicated by low SF concentrations, and the control group was well above the cutoff value of 12 μg/L. Iron supplementation was effective in correcting the anemia of the IDA group but not in restoring the SF to normal concentrations. Supplementation also significantly (P = 0.0001) improved the concentration of SF in the IDP women. We had to reassign one subject with an initial Hb concentration > 120 g/L from the IDP to the IDA group because of an increase of 24 g/L in her Hb concentration after iron supplementation. As expected from our screening criteria, there were no differences in percentage body fat, lean body weight, or body surface area among groups (Table 2). There were no significant differences among the groups with respect to the number of hours fasted before the water bath (means for each group ranged from 8.8 to 10.8 h) or day of the menstrual cycle (means ranging from day 5 to day 11). Plasma estrogen and progesterone measurements (data not shown) verified that water baths were performed while subjects were in the follicular phase of the menstrual cycle.

Exposure to 28 °C water for 100 min (Fig 2) resulted in a significantly lower mean core body temperature in the IDA subjects (36.0 ± 0.2 °C) than in the C (36.2 ± 0.1 °C) or IDP subjects (36.4 ± 0.1 °C). Iron supplementation resulted in a significant improvement in the ability of the formerly anemic subjects to maintain body temperature after 100 min of cool-water exposure such that the IDA and C groups did not differ significantly at 100 min. Interestingly, the IDP subjects had a significantly higher mean core temperature than did the IDA or C subjects after 100 min of cool-water exposure, both before and after iron supplementation.
TABLE 1
Hematologic characteristics of the subjects*

<table>
<thead>
<tr>
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<th>Control (n = 12)</th>
<th>Anemic (n = 10)</th>
<th>Iron depleted (n = 8)</th>
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<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>34.3 ± 11.8*</td>
<td>30.4 ± 14.2b</td>
<td>3.8 ± 2.4c</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>136 ± 9a</td>
<td>137 ± 7*</td>
<td>110 ± 11b</td>
</tr>
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* x ± SD. Pre. before supplementation; post. after supplementation.

Means with different superscripts within a row are significantly different (P<0.05) for pre- vs post-comparisons within a hematologic-characteristic group and for pre-comparisons and post-comparisons across groups.

VO₂ of the three groups of subjects did not differ at baseline before iron supplementation (Fig 3). The IDA subjects did have a significantly lower VO₂ than did the C subjects at 100 min and than the IDP subjects at both 40 and 100 min of cool-water exposure. After the supplementation period, the VO₂ of the IDA women was significantly lower than that of the C women at baseline and at 40 and 100 min of cool-water exposure. Iron supplementation in the IDP women was associated with significant decreases in VO₂ at all three time points in the postsupplementation water baths. Before supplementation, the percentage rise in VO₂ above baseline was significantly less in the IDA than in the C women (64 ± 8% vs 86 ± 7%, respectively; P = 0.04) at 100 min as well as 40 min (30 ± 8% vs 48 ± 7%, respectively; P = 0.03). These differences were not significant at 40 min but remained significantly different at 100 min of exposure (68 ± 9% vs 82 ± 10%, respectively; P = 0.04) in postsupplementation comparisons. The mean RQ ranged from 0.78 to 0.85 for the three groups and did not differ among groups except for a significantly lower RQ in the IDA group at baseline, both before (P = 0.01) and after (P = 0.02) iron supplementation when compared with the C women, and post-supplementation (P = 0.003) when compared to the IDP women.

We calculated the total VO₂ of the subjects during the 100 min of cool-water exposure and converted these data to kilocalories expended during the water bath (Table 3). The IDA women expended ~8% fewer calories than did C women and nearly 17% fewer than did IDP subjects before iron supplementation; the latter difference was statistically significant (P = 0.0004). In addition, the mean kilocalorie expenditure of the IDP women was significantly (P = 0.02) greater than that of the C women, presupplementation. Iron supplementation normalized the caloric expenditure of both iron-deficient groups such that there were no significant differences among the three groups.

In our examination of the potential underlying hormonal changes associated with this poor thermoregulatory capacity in iron deficiency, we focused on the thyroid hormones and catecholamines. Figure 4 shows quite clearly that IDA subjects had significantly lower plasma T₃ concentrations than did the C or IDP women throughout the water baths. These differences persisted even after iron supplementation despite a significant 12% rise in T₃ concentration in the IDA group at baseline after iron therapy. Women with depleted iron stores had significantly lower mean plasma T₃ concentrations than did the C women at baseline and at 40 and 100 min of cool water exposure after the supplementation period.

As shown in Figure 5, plasma T₄ concentrations were also significantly lower in the IDA subjects than the C or IDP subjects throughout the water baths and were not normalized with 3 mo of iron supplementation. Before iron supplementation, the IDP women had a significantly greater mean TSH concentration than did the C women at baseline (data not shown). This difference was not evident at the 40- or 100-min time points or after the iron-supplementation period.

Plasma norepinephrine concentrations did not differ among

![FIG 2. Core temperature response of the 12 control (C), 10 iron-deficient-anemic (IDA), and 8 iron-depleted (IDP) women exposed to a 28 °C water bath before (pre) and after (post) iron supplementation.](https://example.com/figure2.png)

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groups in either the cross-sectional comparisons or the longitudinal comparisons (Fig 6). Similarly, by using log-transformed data to normalize the distributions, we found that plasma epinephrine concentrations were highly variable and generally were not different among groups (Fig 7).

Discussion

This investigation demonstrates clearly that iron-deficiency anemia significantly alters the ability of young women to maintain body temperature when a moderate cold stress is applied. The IDA women had a significantly lower core body temperature after 100 min of cool water exposure and did not increase their metabolic rate as much as did the control women. The nonanemic iron-depleted group in this study actually thermoregulated better than did the control subjects when core body temperature was examined. The obvious contrast to the nonanemic iron-depleted group in the sample of Martinez-Torres et al (14) is that metabolic rates of the subjects. The anemic Venezuelan subjects had significantly higher metabolic rates than did the control subjects after 1 h of cool-water exposure (10.3 vs 5.7 mL·min⁻¹·kg⁻¹), whereas we observed a consistently lower metabolic rate in our women, who were admittedly far less anemic. We surmise that the previously discussed leanness of the South American subjects and perhaps their much greater severity of iron-deficiency anemia significantly perturbed the relationship of iron status to thermoregulation in these subjects.

The nonanemic women with depleted iron stores in this study actually thermoregulated better than did the control subjects when core body temperature was examined. The obvious contrast to the nonanemic iron-depleted group in the sample of Martinez-Torres et al (14) is confounded because of an average 10 g/L lower hemoglobin concentration in their nonanemic group compared with their control group. On the basis of a conceptual model that functional sequelae of iron deficiency occur only when stores are depleted, we would have anticipated some defect in temperature regulation (9, 26). The comparable mean thyroid hormone (ie, T_3 and T_4) concentrations and significantly higher core body temperature in this group of women relative to the control group may thus reflect overcompensatory activity to a defect in some other part of neurohormonal or metabolic activity. This clearly is speculation, however, and remains to be addressed in other studies.

Published studies in both iron-deficient and hypothyroid rats show very poor thermoregulatory capacity (8–12, 27). Iron-de-

![Figure 3. VO₂ response of the 12 C, 10 IDA, and 8 IDP women exposed to a 28 °C water bath both before and after iron supplementation. See Figure 2 for symbol representation. VO₂ of IDA was significantly lower than C (P = 0.04) at 100 min and than IDP at 40 (P = 0.002) and 100 (P = 0.02) min. presupplementation. There was a significant decrease in VO₂ of IDP at baseline (~10) (P = 0.01), 40 (P = 0.05), and 100 (P = 0.03) min after 12 wk of iron supplementation. VO₂ of IDA significantly lower than C at baseline (P = 0.02), 40 (P = 0.03), and 100 (P = 0.006) min. postsupplementation.](attachment:image_url)

**TABLE 3**

Energy expended during the cool water bath*

<table>
<thead>
<tr>
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<th>Control (n = 12)</th>
<th>Anemic (n = 10)</th>
<th>Iron depleted (n = 8)</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Energy expended (kcal)</td>
<td>143.0 ± 16.3*</td>
<td>139.8 ± 21.5*</td>
<td>131.6 ± 25.0*</td>
</tr>
</tbody>
</table>

* X ± SD. Means with different superscripts are significantly different (P < 0.05) for pre- vs post-comparisons within a group and for pre-comparisons and post-comparisons across groups.
concentrations of IDA were significantly lower than were C values at baseline (P < 0.0001 for all three time points) and postsupplementation (P = 0.0001 at baseline and 40 min; P = 0.0008 at 100 min) and than IDP at baseline (P = 0.0001), 40 (P = 0.0001), and 100 (P = 0.0004) min presupplementation and at baseline (P = 0.007) and 40 (P = 0.008) min postsupplementation. With iron supplementation, IDA had a significant increase in plasma T3 concentration at baseline and IDP had a significant decrease in plasma T3 concentration at baseline (P = 0.01) and 40 (P = 0.05) min. IDP had significantly lower plasma T3 concentrations than C at baseline (P = 0.03) and 40 (P = 0.009) and 100 (P = 0.03) min postsupplementation.

Less efficient rats have a less responsive thyroid system as measured by changes in TSH, T4, and T3 concentrations after acute cold exposure (9, 12). The responsiveness was a direct and linear function of severity of anemia up to a plateau point, after which it appeared far less dependent on anemia per se. When iron-deficient-anemic rats were provided with T3 by exogenous means, the rats were able to thermoregulate adequately (10).

FIG 4. Plasma T3 response of the 12 C, 10 IDA, and 8 IDP women exposed to a 28 °C water bath both before and after iron supplementation. See Figure 2 for symbol representation. IDA had significantly lower plasma T3 concentrations than did C both pre- (P = 0.0001 for all three time points) and postsupplementation (P = 0.0001) at baseline and 40 min; P = 0.0008 at 100 min) and than IDP at baseline (P = 0.0001), 40 (P = 0.0001), and 100 (P = 0.0004) min presupplementation and at baseline (P = 0.007) and 40 (P = 0.008) min postsupplementation. With iron supplementation, IDA had a significant (P = 0.02) increase in plasma T3 concentration at baseline and IDP had a significant decrease in plasma T3 concentration at baseline (P = 0.01) and 40 (P = 0.05) min. IDP had significantly lower plasma T3 concentrations than C at baseline (P = 0.03) and 40 (P = 0.009) and 100 (P = 0.03) min postsupplementation.

The present study in humans thus provides a certain degree of interpretation. Animal studies have suggested a strong dependency of the peripheral sympathetic nervous system activity on the severity of iron deficiency (8, 11, 13). In contrast, to the study of Martinez-Torres et al (14) and some of the studies of urinary catecholamine excretion in iron-deficient infants (28), we observed no consistent effect of iron-deficiency anemia on plasma catecholamine concentrations. Thus, in spite of clear data on changes in norepinephrine turnover in iron-deficient rats (8, 29), this study cannot provide any data that would support this as a functional consequence in humans.

More recently, we used a less complex situation than cold stress to examine the responsivity of the thyroid system as a function of iron nutriture (12). After injection of graded doses of thyroid-releasing hormone (TRH), iron-deficient-anemic rats had a blunted and delayed TSH, T4, and T3 response; in addition, the turnover rate of T3 in plasma was ~50% of normal. Thus, while a direct causal relationship is not established in the present study, it seems reasonable that an alteration in thyroid hormone metabolism plays a role in poor thermoregulation in iron-deficiency anemia.

FIG 6. Plasma norepinephrine response of the 12 C, 10 IDA, and 8 IDP women exposed to a 28 °C water bath both before and after iron supplementation. See Figure 2 for symbol representation.

FIG 5. Plasma T4 response of the 12 C, 10 IDA, and 8 IDP women exposed to a 28 °C water bath both before and after iron supplementation. See Figure 2 for symbol representation. Plasma T4 concentrations of IDA were significantly lower than were C values at baseline (P = 0.001) and at 40 and 100 min (P = 0.002) and than IDP at baseline and 40 min (P = 0.003) and 100 min (P = 0.006).

FIG 7. Plasma epinephrine response of the 12 C, 10 IDA, and 8 IDP women exposed to a 28 °C water bath both before and after iron supplementation. See Figure 2 for symbol representation. Plasma epinephrine values represent log-transformed data reconverted to original units. SEM bars have been omitted for this variable because of difficulty of interpretation.
of agreement with the animal studies but does not clarify the issue of the dependency of impaired thermoregulation in subjects with anemia. The failure to completely normalize the concentrations of T₄ or T₃ and to completely correct the poor thermoregulatory performance of the anemic women with 12 wk of 79 mg elemental Fe supplementation/d was disappointing. We feel this is most likely related to our failure to completely and fully replenish the iron stores of the anemic subjects despite the correction of their anemia. Unpublished data from our laboratory and the data of Dillman et al (10) demonstrate that iron dextran treatment in rats normalizes thyroid hormone concentrations, sympathetic nervous system activation, and thermoregulatory capacity within 3–7 d of injection, thus proving the reversibility of these defects. We found it unfeasible to require the subjects to come to the laboratory each day to receive their iron supplement, and we used no direct measures of compliance during the supplementation phase. Thus, although complete normalization of function with repletion was not demonstrated in the present study, animal experiments suggest that function is restored with iron repletion. This experiment was designed to examine thermoregulatory performance in iron deficiency as a tool for asking questions about the impact of iron deficiency on energy metabolism. Because many of the same neurohormonal systems that alter metabolic rate and heat production during cold stress also govern resting metabolic rates in everyday life, these data suggest to us that thyroid-hormone-dependent energy metabolism is significantly altered in iron-deficient-anemic humans. These data also challenge the notion that the catecholaminergic limb of the metabolic machinery is altered in iron-deficient humans, although further studies of subjects with a greater range of iron-deficiency anemia may prove otherwise.

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References