Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores

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ABSTRACT We assessed the importance of lean and fat tissue depletion as determinants of the adaptive reduction in basal metabolic rate (BMR) in response to food deprivation by reanalyzing the data on BMR and body composition for the 32 men participating in the classic Minnesota experiment of semistarvation and refeeding. We used individual data on BMR, body fat, and fat-free mass (FFM) assessed during the control (prestarvation) period, at weeks 12 and 24 of semistarvation (S12 and S24), and week 12 of restricted refeeding (R12) to calculate an index of the reduction in thermogenesis at S12, S24, and R12, defined as the change in BMR adjusted for changes in FFM and fat mass, and an index of the state of depletion of the fat mass and FFM compartments at these times, defined as the deviation in fat mass or FFM relative to control values. The results indicated a positive relation between the reduction in thermogenesis and the degree of fat mass depletion (but not FFM depletion) during weight loss as well as during weight recovery \( r = 0.5, P < 0.01 \). Furthermore, the residual variance was predicted by the initial (prestarvation) percentage fat and the corismic index (sitting height/height). Taken together, these results in normal-weight men responding to severe food deprivation reveal anthropometric predictors for human interindividual variability in the capacity for energy conservation and suggest that the adaptive reduction in BMR is partly determined by an autoregulatory feedback control system linking the state of depletion of fat stores to compensatory mechanisms that suppress thermogenesis.

KEY WORDS Thermogenesis, malnutrition, obesity, energy balance, basal metabolic rate, men, semistarvation

INTRODUCTION It is well established from longitudinal studies of human starvation and semistarvation that weight loss is accompanied by a decrease in basal metabolic rate (BMR) greater than can be accounted for by the changes in body weight or body composition (1–5). This deviation from predicted values in the reduction of BMR is generally regarded as the outcome of a regulatory process that, in the face of food energy deficits, increases metabolic efficiency by suppressing thermogenesis and hence reduces the rate at which the body’s tissues are being depleted.

Although the survival value of such an energy-sparing regulatory process that limits tissue depletion during food scarcity is obvious, there are considerable uncertainties concerning its nature and functional significance. First, the factors that signal and dictate the pattern of this suppression of thermogenesis during weight loss remain elusive. Although it is generally accepted that it is an early and prompt response to reduced food energy flux per se (6), the extent to which it may also be determined by the depletion of lean or fat tissues is unknown. Second, it is not clear whether the energy thus conserved during weight loss is directed specifically at sparing protein, fat, or both tissue compartments. Although the rate of urinary nitrogen loss is known to decrease during prolonged starvation, there are no quantitative data supporting such a relation between reduced thermogenesis and a specific sparing of protein during weight loss. Third, the results of a few longitudinal studies that have examined a possible link between reduction in thermogenesis and the extent of body fat depletion in obese subjects have been equivocal, with one study reporting a significant correlation between the size of fat loss and the reduction in BMR [after adjustment for changes in fat-free mass (FFM)] (7) but others reporting no difference in FFM-adjusted BMR between 2 levels of fat loss (5, 8). In the last-mentioned studies, however, the number of subjects was small, the extent of fat depletion was not too severe, or the measurements were conducted after weight stabilization rather than during the dynamic process of losing weight. Furthermore, the association between reduced thermogenesis and fat depletion have been examined only in obese patients undergoing therapeutic dieting, and results of similar analyses have not been reported in normal-weight (nonobese) subjects during weight loss.

During weight recovery, by contrast, our recent reanalysis of the data from the Minnesota experiment of semistarvation and refeeding in healthy normal-weight men (2) revealed that the reduction in thermogenesis during semistarvation persists after 12 wk of restricted refeeding, with its size being inversely proportional to the degree of fat recovery but unrelated to the degree of FFM recovery (9). A similar relation between the size of suppression of thermogenesis and the recovery of body fat (and not FFM) was recently reported in patients recovering from malnu-

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trition resulting from nonneoplastic gastrointestinal disease (10). Such findings support the notion that during weight recovery a component in the economy in thermogenesis is directed specifically at accelerating the replenishment of fat stores (11), thereby underlying the common observation of a disproportionate rate in the recovery of body fat relative to lean tissue after weight loss (2, 12–16). More direct support for this contention can be derived from energy balance studies in laboratory animals regaining weight after food restriction (17, 18). Under conditions whereby the refed animals were pair fed with weight-matched controls, the rate of protein deposition was the same as in the controls but that of fat deposition was increased by 3-fold as a result of energy spared from a 10–15% lower energy expenditure during the early phase of weight recovery (18).

In the light of these observations from refeeding studies, the possibility arises that an important component in the economy in thermogenesis could be a control system operating as a continuum during both weight loss and weight recovery to spare energy specifically as a function of the state of depletion of the fat stores. To test this hypothesis, we conducted a further reanalysis of data on BMR and body composition of the 32 men in the Minnesota experiment during weight loss and weight recovery. Our main objective was to determine whether the relation between reduced thermogenesis and body fat, previously reported during weight recovery, also occurs during weight loss. We also examined whether anthropometric measures (before weight loss) could predict the component of suppressed thermogenesis that is unrelated to fat store depletion.

SUBJECTS AND METHODS

General features of the Minnesota experiment

Subjects

The 32 subjects were young, healthy white men, aged 25 ± 4 y (x ± SD; range: 20–33 y), whose physical characteristics before semistarvation were as follows: height, 179 ± 6 cm (range: 167–192 cm); body weight, 69.4 ± 5.8 kg (range: 62–83.6 kg); and body fat, 14 ± 5% (range: 6–25%).

General experimental design

The 32 men resided continuously at the University of Minnesota during the 12-wk control baseline period (C1–C12); the 24 wk of semistarvation (S1–S24), during which each man lost ≈25% of his initial body weight; and the 12 wk of restricted refeeding (R1–R12) before ad libitum refeeding. At the beginning of restricted refeeding, the 32 men were divided into 4 groups (Z, L, G, and T) on the basis of the energy value of the rehabilitation diets, which differed by equivalent steps of L, G, and T) on the basis of the energy value of the rehabilitation of restricted refeeding, the 32 men were divided into 4 groups (Z, L, G, and T). Each energy group was subdivided into subgroups receiving either extra protein and vitamins, or placebo. Except that more of each food item was given. Groups Z, L, G, and T were refed different amounts of energy, but even in the highest energy group (T) energy intakes were still deficient relative to intakes during the control period. During this restricted refeeding period, 12–17% of energy was provided as protein, 20% as fat, and 63–68% as carbohydrate.

Tests and measurements

Body weight was measured on a beam balance and body fat was determined by hydrodensitometry. Corrections of body fat mass and FFM for increased hydration and the relative mass of bone at the end of semistarvation and during refeeding were possible with formulas provided by Keys et al (2). Corrections were derived from a small group of the Minnesota men in whom extracellular fluid space was determined at the end of semistarvation and at frequent intervals during refeeding by the thiocyanate dilution technique. BMR was assessed from the rate of oxygen consumption during the control period (C12), at the midpoint of semistarvation (S12), at the end (S24) of semistarvation, and at the end of restricted refeeding (R12).

Present data analysis

Index of reduction in thermogenesis

The BMR of each of the 32 men at C12, S12, S24, and R12 was calculated in kJ/d from oxygen consumption data by using the conversion factor of 20.5 kJ/L oxygen. After testing whether the reduction in BMR at each of the times during semistarvation and refeeding was significantly greater than that explained by changes in FFM and fat mass (by analysis of covariance, with FFM and fat mass as covariates), the size of this greater-than-predicted reduction in BMR was then estimated for each individual as the reduction in BMR (relative to that at C12) after adjusting for the changes in FFM and fat mass. The coefficients for adjusting FFM and fat mass were obtained from the relation among the BMR, FFM, and fat mass of the Minnesota men during the control baseline period (at C12), namely:

\[
\text{BMR (kJ/d)} = 3482 + 52.9 \text{FFM} + 9.7 \text{fat mass} \]

The methods for calculating the total thermogenic economy in absolute terms (kJ) or as a percentage of the control baseline BMR at C12 are described by the following equations:

\[
\text{Total thermogenic economy}_{wk} (kJ) = (\text{BMR}_{wk} - \text{BMR}_{c12}) - (\Delta \text{FFM}_{wk} 52.9 + \Delta \text{Fat}_{wk} 9.7) \]

\[
\text{Total thermogenic economy}_{wk} (%) = \left( \frac{(\text{total thermogenic economy}_{wk} \times 100)}{\text{BMR}_{c12}} \right)
\]

This method of estimating total thermogenic economy (adaptive reduction in BMR) takes into consideration individual variability in BMR during the baseline period (at C12) and hence better controls for interindividual differences. However, the coefficients for FFM and fat mass are derived on the basis of a between-subject relation among BMR, FFM, and fat mass but are assumed...
to describe a within-subject relation among these 3 variables. They are therefore taken as the reference coefficients for adjusting changes in FFM and fat mass in the estimation of the adaptive reduction of BMR during starvation and refeeding. This is an adequate assumption for the purpose of our analysis centered on examining the predictors of variability in the size of adaptation in BMR rather than the absolute size of adaptation per se.

Index of the state of depletion of the fat mass and FFM compartments

An index of the state of depletion of the fat or FFM compartment (referred to as deviation in body fat mass or FFM) was determined at S12, S24, and R12 and was expressed as a percentage difference from the corresponding control (C12) value. These data were calculated by using the following equations:

\[
\text{Deviation in fat (\% of control)} = \frac{(\text{Fat}_{wk} - \text{Fat}_{C12})}{\text{Fat}_{C12}} 
\times 100
\]

\[
\text{Deviation in FFM (\% of control)} = \frac{(\text{FFM}_{wk} - \text{FFM}_{C12})}{\text{FFM}_{C12}} 
\times 100
\]

where wk is S12, S24, or R12.

Index of deficit in food energy intake

The deficit in energy intake for each individual at the midpoint (S12) and end (S24) of semistarvation and during restricted refeeding (at R12) was calculated as the percentage difference of energy intake (EI_{wk}) at these times from habitual energy intake during the control period (EI_{C}); the latter was taken as the amount of energy consumed by the subject during the last 3 wk of the control period. The deviation in energy intake was calculated by using the following equation:

\[
\text{Deviation in food energy intake (\% of control)} = \frac{(\text{EI}_{wk} - \text{EI}_{C})}{\text{EI}_{C}} 
\times 100
\]

where wk is S12, S24, or R12.

Statistical analysis

Statistical analyses were performed by using the computer software program STATISTIK (version 4.0; Analytical Software, St Paul). The various linear model procedures used were the analysis of variance-covariance (repeated-measure design) for testing differences between BMR at each time during semistarvation and refeeding and that during the control baseline period, with FFM and fat mass as covariates; Pearson product-moment correlations for determining linear associations between variables; partial correlation procedures for computing the residual correlation between variables after controlling for the effects of another set of variables; and simple, multiple, and stepwise regression analyses.

RESULTS

BMR after adjusting for changes in FFM and fat mass

The analysis of covariance of BMR during semistarvation and refeeding, with FFM and fat mass as covariates, indicated that BMR at S12, S24, and R12 remained significantly different from BMR during the control period (C12), even after controlling for

| Table 1 |
| Analysis of variance and covariance of basal metabolic rate (BMR) during starvation and refeeding |
| Semistarvation | Refeeding: |
| S12 | S24 | R12 |
| (4570 ± 436 kJ/d)² | (4104 ± 414 kJ/d) | (5396 ± 467 kJ/d) |
| Analysis of variance | 579² | 916² | 210² |
| With FFM as covariate | 476² | 380² | 10² |
| With FFM and fat | 707² | 604² | 8² |

²BM in parentheses.

³P < 0.001.

⁴P < 0.01.

FFM alone or for both FFM and fat mass [P < 0.001 at the times during semistarvation (S12 and S24) and P < 0.01 during refeeding at R12; Table 1]. These results therefore suggest that the reductions in BMR at S12, S24, and R12 were significantly greater than predicted from the changes in FFM and fat mass and hence provide evidence for an adaptive reduction in BMR (reduced thermogenesis) during the dynamic phase of weight loss, at the new equilibrium of lower body weight, as well as during weight recovery under conditions of restricted refeeding.

Variability in size of the adaptive reduction in BMR

The central tendency and variability in the size of reduction in BMR adjusted for the change in FFM and fat mass (the total thermogenic economy) expressed in absolute terms (kJ) or as a percentage of control baseline BMR at C12 are presented in Figure 1; the mean and SD of these values are provided in the legend. At S12 the median and mean adjusted BMRs were lower than the control BMR by ≈20%, and this value dropped further to ≈25% at week S24, which corresponds to a relatively static phase of lower weight maintenance. After 12 wk of restricted refeeding, the median and mean values for adjusted BMR were still below control values by ≈10%. The interindividual variability in the reduction in adjusted BMR was large at all times, with CVs of 32%, 25%, and 67% at S12, S24, and R12, respectively.

Relation between total thermogenic economy and tissue depletion during dynamic phases of weight loss and weight recovery

The extent to which fat mass and FFM depletion were determinants of the change in adjusted BMR (total thermogenic economy) was then examined during the dynamic phases of weight loss (S12) and during weight recovery (R12). As shown in Figure 2, the change in adjusted BMR plotted against the deviation in body fat revealed a positive relation both during the dynamic phase of semistarvation and at the end of restricted refeeding: the greater the percentage reduction in body fat, the greater the reduction in adjusted BMR and hence the greater the total thermogenic economy. These significant correlations between the total thermogenic economy and fat deviation at S12 (r = 0.47, P < 0.01) and at R12 (r = 0.49, P < 0.01) contrasted with the lack of significant correlation against the deviation in FFM, whether at
S12 or at R12 (Table 2). The results are similar whether the total thermogenic economy, assessed as the change in adjusted BMR, is expressed in absolute terms (kJ) or as a percentage of BMR during the control period. Furthermore, the relation between the total energy economy and fat deviation, whether at S12 or at R12, was also unaltered after controlling (by partial correlation analysis) for variance in the deficit in food energy intake.

Relation between the residual thermogenic economy at S12 and R12

Because the relation between the total thermogenic economy and fat depletion during weight loss persisted during subsequent weight recovery, we also examined the extent to which the variance in the residuals of this relation with fat deviation during weight loss was conserved during weight recovery. As shown in

FIGURE 1. The distribution of values for the change in basal metabolic rate (BMR) adjusted for fat-free mass and fat mass (ie, total thermogenic economy) after 12 wk (S12) and 24 wk (S24) of semistarvation and after 12 wk of restricted refeeding (R12). The data are presented in absolute terms (left panel) and in relative terms (right panel; ie, expressed as a percentage of the control baseline BMR at C12). Each box encloses the data from the second and third quartiles (ie, data between the lower quartile, LQ, and the upper quartile, UQ) and is bisected by a line at the value for the median. The tip of vertical lines at the top and bottom of the box indicate the minimum and highest maximum values, respectively. Open circles are extreme values. The mean (±SD) values for panel A are 1491 ± 514, 1706 ± 477, and 693 ± 464 kJ and for panel B are 21.5 ± 6.9%, 24.7 ± 6.2%, and 9.7 ± 6.6% for S12, S24, and R12, respectively.

FIGURE 2. Relation between altered thermogenesis (total thermogenic economy), assessed as the change in basal metabolic rate (BMR) adjusted for fat-free mass (FFM) and fat mass (relative to the control value for BMR at C12) and the state of depletion of body fat stores (assessed as the deviation in body fat relative to the control value) during weight loss (S12, week 12 of semistarvation) and during weight recovery (R12, week 12 of restricted refeeding). These relations between total thermogenic economy and fat deviation, both at S12 and R12, contrast with the lack of correlation against deviation in FFM (correlation and regression coefficients data are shown in Table 2).
Refeeding (R12)
Deviation in fat mass 0.48 7.33 2.48 2
Deviation in FFM 0.23 41.3 ± 31.5

Semistarvation (S12)
Deviation in fat mass 0.45 9.93 ± 3.55
Deviation in FFM −0.25 −39.0 ± 26.6

Regression and partial correlation analyses between changes in adjusted basal metabolic rate (BMR; total thermogenic economy) and the deviation in body fat or in fat-free mass (FFM) during the dynamic phase of semistarvation (S12) and refeeding (R12)1.

TABLE 3
Regression and correlation analyses between changes in adjusted basal metabolic rate (BMR; total thermogenic economy) at the end of semistarvation (S12) and refeeding (R12) versus S12 showed a significant correlation (r = 0.52, P < 0.001); the correlation was also significant for data of residual thermogenic economy expressed on an absolute basis (r = 0.57, P < 0.001).

Relation between total thermogenic economy and tissue depletion during the static phase of lower weight maintenance

We next examined whether at the end of semistarvation (at S24), a period characterized by little or no change in body weight, a relation between the total thermogenic economy and fat deviation could also shown. The results indicated no significant correlation between the total thermogenic economy and fat mass or FFM deviation at S24 (Table 3). However, because the residual thermogenic economy at S12 was significantly correlated with that during refeeding at R12 (Figure 3), a continuum may exist in the variance of residual thermogenic economy found at S12 and persisting through S24 and during the phase of restricted refeeding. Indeed, after the variance in the residual thermogenic economy at S12 was controlled for, a significant correlation between the total thermogenic economy and the deviation in fat became evident at S24 (r = 0.4, P < 0.05; Table 3). This marked improvement in correlation and regression coefficients at S24, specifically vis-à-vis deviation in body fat mass and not that of FFM, was also evident during refeeding, when the total thermogenic economy at R12 was controlled by the residual thermogenic economy at S12 (Table 3).

Predictors of variance in thermogenic economy not associated with tissue depletion

To find predictors for the interindividual variability in the thermogenic economy not associated with fat depletion, the residual thermogenic economy at S12 was correlated with several anthropometric measurements during the control period, namely height, sitting height, corneal index (ratio of sitting height to height), body weight, body fat, body fat as a percentage of body weight, FFM, body mass index, and abdominal circumference. The results are shown in Table 4. By simple regression analysis, the corneal index, fat mass, percentage fat, body mass index, and abdominal circumference were found to be significantly correlated with the residual thermogenic economy. By stepwise regression analysis, however, the residual thermogenic economy was found to be strongly predicted only by the

TABLE 2
Regression and correlation analyses between changes in adjusted basal metabolic rate (BMR; total thermogenic economy) at end of semistarvation (S24) or refeeding (R12) and the deviation in body fat (or in fat-free mass), controlled for the effects of residual thermogenic economy at S24 or refeeding (R12) and the deviation in body fat (or in fat-free mass), controlled for the effects of residual thermogenic economy at S12:

Table 3. By simple regression analysis, the corneal index, fat mass, percentage fat, body mass index, and abdominal circumference were found to be significantly correlated with the residual thermogenic economy. By stepwise regression analysis, however, the residual thermogenic economy was found to be strongly predicted only by the

FIGURE 3. Relation between the residual thermogenic economy (assessed as the total thermogenic economy adjusted for fat depletion) during weight loss (S12, week 12 of semistarvation) and during weight recovery (R12, week 12 of restricted refeeding).
initial (prestarvation) percentage body fat, followed by the cormic index; furthermore, these 2 independent variables together resulted in an $r^2$ of 0.42 or 0.46 and hence explained nearly half of the variance in the residual thermogenic economy.

**Additional data analysis**

For the various relations described above, statistical analysis of the data obtained on the basis of fat mass and FFM not corrected for excess hydration and relative bone mass or adjustments of changes in BMR by using coefficients for fat mass and FFM derived from much larger population samples (19, 20) yielded similar results and correlation coefficients. These results are therefore not shown.

**DISCUSSION**

Although it is generally accepted that the adaptive reduction in BMR (ie, suppression of thermogenesis) during weight loss is a relatively prompt response to a marked decrease in food energy flux, it has long been suspected that the size of this energy-sparing phenomenon is also determined by the extent to which the body’s tissues are depleted. However, it has been difficult to differentiate the effect of tissue depletion from that of reduced food intake in the reduction in thermogenesis in humans because this requires the longitudinal assessment of changes in BMR and body composition before and during the course of substantial changes in body weight. To our knowledge, the Minnesota experiment is the only study that satisfies these criteria in normal-weight humans and thus is a unique study for gaining insights into the normal physiologic responses to food deprivation (2).

We reanalyzed the individual data for the changes in BMR and body composition of the 32 men subjected to a ~50% reduction in their habitual food intake. Evidence presented here shows that in response to such severe food deprivation, the amount of reduction in thermogenesis during weight loss is largely predicted by the degree of body fat depletion. The relation observed between the change in adjusted BMR and fat depletion, suggesting that the greater the degree of fat depletion, the greater the suppression of thermogenesis, was shown to exist during both weight loss and weight recovery. This continuum in the existence of this relation between suppressed thermogenesis and fat depletion during these 2 phases of dynamic changes in body weight, coupled with the demonstration of its specificity to fat depletion (because no relation was observed with FFM depletion) may reflect the operation of a control system with a negative feedback loop between a component of regulatory thermogenesis and the state of depletion of the fat stores.

This continuum in energy conservation during weight loss and weight recovery is also found in the variance of suppressed thermogenesis unrelated to fat depletion (ie, in the residual thermogenic economy), as judged by the significant correlation observed between the residual thermogenic economy during weight loss (at S12) and that during weight recovery (at R12). This is further substantiated by the fact that the correlation obtained between the total thermogenic economy and fat depletion either during refeeding (at R12) or at the end of the semistarvation period (at S24) was either markedly improved or was revealed, respectively, after adjusting for the variance in the residual thermogenic economy at the midpoint of semistarvation (at S12).

The difficulty in demonstrating a direct relation (ie, by simple regression) between adjusted BMR and fat depletion at the end of semistarvation (S24) most probably was because many of the men were severely emaciated. Under these conditions, the data on BMR and body composition were most difficult to interpret because of 1) the presence of edema of varied severity in many of the subjects, 2) the greater likelihood for major changes in the ratio of the visceral mass to lean tissue mass, and 3) the confounding effect of changes in thermal regulation in response to an increase in surface-to-volume ratio and loss of body fat (and hence insulation) in the many severely depleted subjects. (Indeed, whereas oral temperature dropped in every subject at S12, it rose back to prestarvation values in most of the men at S24.) Furthermore, the subjects were actively losing weight at S12 whereas at S24 their body weight was relatively stable. In light of data suggesting that the process of losing weight results in a lower resting metabolic rate than when body weight is stabilized at a lower level (5), such differences in the dynamics of weight changes between S12 and S24, as well as uncertainties about the precision of the maintenance of the composition of body weight at S24, could also be confounding factors in the interpretation of BMR data at S24.

For these reasons, the variance in the change in adjusted BMR at the midpoint of semistarvation (at S12) may provide a more reliable indication of the true biological differences among the subjects in their capacity for energy conservation via the suppression of regulatory thermogenesis. The examination of anthropometric predictors for suppressed thermogenesis not associated with fat depletion reveals that the cormic index and the initial percentage of body fat together explained nearly 50% of the variance in the thermogenic variable. The physiologic significance of anthropometric predictors is uncertain, but it is interesting that these 2 independent variables can be related to body composition, namely the percentage fat reflecting the ratio of fat to lean tissue compartment and the cormic index perhaps reflecting the ratio of metabolically fast organs and tissues in the upper body portion (ie, sitting height) to the metabolically slow skeletal muscle mass, which is well correlated with height (21).
The depletion of fat stores is a biphasic response to starvation stress, but that there is also a slower one. This suggests that in response to severe food deprivation, the common observation of a disproportionate rate of fat relative to lean tissue deposition during weight recovery after experimental starvation (2) or pathophysiologic cachectic conditions (12–16) and may also play a role in the relapse of obesity after therapeutic slimming (23, 24).

The present analysis addresses only the possible link between tissue depletion and reductions in regulatory thermogenesis in the BMR compartment (i.e., energy expenditure at rest). Still to be investigated is the extent to which the economy in energy expenditure associated with reduced physical activity during food deprivation (2, 25) might also have a component of suppressed thermogenesis that is related to the degree of fat depletion. Furthermore, although the various components of the loops that constitute these 2 control systems for regulatory thermogenesis (at least in the compartment of resting metabolic rate) remain to be elucidated, it is of interest to draw a parallel between the present findings of a relation between suppressed thermogenesis and fat depletion and our previous demonstration (also from data from the Minnesota experiment) of a similar relation between post-starvation hyperphagia and fat depletion (26, 27). These relations are therefore consistent with the existence, in humans, of autoregulatory feedback signals linking the state of depletion of fat stores to compensatory mechanisms operating via both food intake and regulatory thermogenesis.

Thus, the cormic index may be a crude index of individual variability in the metabolic composition of the FFM.

To what extent these predictors are indicative of genetic variability contributing to the variance in the suppression of thermogenesis in the response to food deprivation is unknown. However, the negative correlation between the initial degree of fatness and the suppression of thermogenesis unrelated to fat depletion suggests that in response to food deprivation, the leaner the person, the greater the capacity to conserve energy through suppression of thermogenesis. Conversely, the more obese the person, the lesser the suppression in thermogenesis for the same degree of body fat depletion, a contention that seems to be in line with a cross-comparison of studies indicating that, in general, the size of the adaptive fall in BMR tended to be less marked in obese than in lean individuals (22).

In conclusion, while remembering the homogeneous nature and relatively few participants in the Minnesota experiment and hence using caution in data interpretation, this extension of our reanalysis of individual data on BMR and body composition of the Minnesota men reveals several anthropometric predictors for human interindividual variability in the reduction in thermogenesis in response to severe food deprivation. It also suggests that not only is the suppression of regulatory thermogenesis a prompt response to the starvation stress, but that there is also a slower response, the size of which may be determined by the degree of depletion of the fat stores. Such a biphasic response in energy conservation to food deprivation raises the possibility that 2 distinct control systems for regulatory thermogenesis underlie energy conservation in humans, a concept depicted in Figure 4. One control system is a direct function of food intake and responds relatively rapidly to starvation stress by functioning as a buffer against energy imbalance and hence spares both lean and fat tissue compartments; it is referred to as nonspecific thermogenesis. The other control system (the size of which is determined only by the degree of fat depletion) has a much slower onset of action by virtue of its relation with the state of depletion of the fat stores; its function is specifically to spare body fat when fat stores become severely depleted and to ensure its rapid replenishment with increased food availability; it is referred to as fat-specific thermogenesis. The sustained suppression of this latter type of regulatory thermogenesis may explain, at least in part, the common observation of a disproportionate rate of fat relative to lean tissue deposition during weight recovery after experimental starvation (2) or pathophysiologic cachectic conditions (12–16) and may also play a role in the relapse of obesity after therapeutic slimming (23, 24).

The present analysis addresses only the possible link between tissue depletion and reductions in regulatory thermogenesis in the BMR compartment (i.e., energy expenditure at rest). Still to be investigated is the extent to which the economy in energy expenditure associated with reduced physical activity during food deprivation (2, 25) might also have a component of suppressed thermogenesis that is related to the degree of fat depletion. Furthermore, although the various components of the loops that constitute these 2 control systems for regulatory thermogenesis (at least in the compartment of resting metabolic rate) remain to be elucidated, it is of interest to draw a parallel between the present findings of a relation between suppressed thermogenesis and fat depletion and our previous demonstration (also from data from the Minnesota experiment) of a similar relation between post-starvation hyperphagia and fat depletion (26, 27). These relations are therefore consistent with the existence, in humans, of autoregulatory feedback signals linking the state of depletion of fat stores to compensatory mechanisms operating via both food intake and regulatory thermogenesis.

FIGURE 4. Schematic representation of the concept of 2 distinct types of regulatory thermogenesis for energy conservation. In response to a step change (reduction) in food intake there is a relatively rapid decrease in thermogenesis, which is then followed by further reduction in thermogenesis as fat is depleted. We propose that the early reduction in thermogenesis functions as a buffer against energy imbalance and conserves energy for the sparing of both lean and fat tissue compartments; it is hence referred to as nonspecific thermogenesis. By contrast, the later reduction in thermogenesis (a function of the degree of depletion of the fat stores) functions to spare specifically the fat stores and to accelerate its rapid replenishment; it is hence referred to as fat-specific thermogenesis.

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