Role of Nonexercise Activity Thermogenesis in Resistance to Fat Gain in Humans

James A. Levine, Norman L. Eberhardt, Michael D. Jensen*

Humans show considerable interindividual variation in susceptibility to weight gain in response to overeating. The physiological basis of this variation was investigated by measuring changes in energy storage and expenditure in 16 nonobese volunteers who were fed 1000 kilocalories per day in excess of weight-maintenance requirements for 8 weeks. Two-thirds of the increases in total daily energy expenditure was due to increased nonexercise activity thermogenesis (NEAT), which is associated with fidgeting, maintenance of posture, and other physical activities of daily life. Changes in NEAT accounted for the 10-fold differences in fat storage that occurred and directly predicted resistance to fat gain with overfeeding (correlation coefficient = 0.77, probability < 0.001). These results suggest that as humans overeat, activation of NEAT dissipates excess energy to preserve leanness and that failure to activate NEAT may result in ready fat gain.

Weight gain occurs in healthy adults when energy intake persistently exceeds energy expenditure. Some individuals appear to increase energy expenditure in response to overeating without increasing volitional exercise and thus maintain a stable body weight. This interindividual variation in weight gain with overfeeding (1, 2) suggests that a thermogenic mechanism or mechanisms may be activated to prevent weight gain or obesity.

When humans are overfed, more than 85% of the stored excess energy is deposited as lipid (3), primarily triglycerides. Lipid is ideally suited for long-term energy storage in mammals; it is caloric-dense and hydrophobic, so that storage occurs without water accumulation. In the presence of persistent, positive energy balance, enormous quantities of triglyceride can be stored through increases in adipocyte size and number (4, 5). Even lean individuals store enough fat to meet energy requirements for more than 1 month, whereas some obese individuals have fat stores that would exceed energy requirements for a year (6, 7). However, why some people appear to accumulate adipose tissue more efficiently than others is unclear (8).

The efficiency of energy storage is calculated by dividing the excess calories stored by the excess calories consumed. Energy storage efficiency can never equal unity because heat transfer is not perfect. An energy efficiency of zero would indicate that all excess energy consumed is dissipated through increased energy expenditure. It has been argued that efficient energy storage is beneficial because it allows longer survival during famine. However, for many Western populations, where food supply is abundant and readily available, efficient energy storage predisposes to obesity, the accumulation of excess body fat. Obesity affects more than one-third of the U.S. population and is a major public health concern because it is associated with diabetes, hypertension, hyperlipidemia, and cardiovascular disease (9).

Some humans appear to resist fat gain with overeating, whereas others readily store excess fat. These subjective observations have been confirmed by a small number of clinical studies that document a small interindividual variation in fat accumulation with overfeeding (1, 2, 10). However, the thermogenic adaptation that allows some individuals to resist weight gain despite overeating has not been identified.

To address this question, we designed a study that allowed us to identify which component or components of energy expenditure showed enough variability to account for the variability in resistance to fat gain during overfeeding. Sixteen nonobese adults (12 males and 4 females, ranging in age from 25 to 36 years) underwent measures of body composition and energy expenditure before and after 8 weeks of supervised overfeeding by 1000 kcal/day. Body composition was measured with dual energy x-ray absorptiometry (DXA) (11), and total daily energy expenditure was measured with doubly labeled water (10, 12). The latter procedure required the administration of water containing

Table 1. Energy partitioning in 16 healthy human volunteers who were fed 1000 kcal/day (4.2 MJ) in excess of weight maintenance requirements for 8 weeks. Additional data are available at www.sciencemag.org/feature/data/982662.shl.

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Mean</th>
<th>Range</th>
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<tr>
<td>Baseline weight (kg)</td>
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<td>Overfed weight (kg)</td>
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<td>58.8–93.1</td>
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<tr>
<td>Weight gain (kg)</td>
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<td>1.4–7.2</td>
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<tr>
<td>Fat gain (kcal/day)*</td>
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<td>58–687</td>
</tr>
<tr>
<td>Fat-free mass gain (kcal/day)*</td>
<td>43</td>
<td>15–78</td>
</tr>
<tr>
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<td>2265–3785</td>
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<tr>
<td>Baseline resting energy expenditure (kcal/day)</td>
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<td>1470–1990</td>
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<tr>
<td>Overfed resting energy expenditure (kcal/day)</td>
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<td>1460–2040</td>
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<td>Baseline thermic effect of food (kcal/day)</td>
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<tr>
<td>Baseline total energy expenditure (kcal/day)</td>
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<tr>
<td>Overfed total energy expenditure (kcal/day)</td>
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<td>2508–4601</td>
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*Energy contents of tissues were calculated with published constants (3).
isotopes of oxygen and hydrogen to the volunteers and measurement of the clearance of the two isotopes from the body. The difference in clearance of the two isotopes represents carbon dioxide production (10, 12), which in turn reflects energy expenditure. These measurements allowed us to observe how overeating affects energy partitioning (Table 1). On average, 432 kcal/day of the excess energy ingested was stored and 531 kcal/day was dissipated through increased energy expenditure, thereby accounting for 97% of the additional 1000 kcal/day (implying optimal compliance). Fat gain varied 10-fold among our volunteers, ranging from a gain of only 0.36 kg to a gain of 4.23 kg, and was inversely related to the increase in total daily energy expenditure ($r = -0.86$, $P < 0.0001$).

Total daily energy expenditure is composed of basal metabolic rate (BMR), postprandial thermogenesis, and physical activity thermogenesis. BMR is the rate at which energy is expended when an individual is laying down at rest in the postabsorptive state. We assessed BMR by using indirect calorimetry to measure oxygen consumption and carbon dioxide production (13). Changes in BMR would be unlikely to account for the 10-fold variance in fat gain among our volunteers because previous investigators have found only modest increases (~10%) with overfeeding (10, 14). In our study, BMR increased by an average of 5% in response to overfeeding (Table 2), accounting for 8% of the excess ingested energy. Thus, the interindividual changes in BMR did not account for the variability in fat gain (Fig. 1A).

Postprandial thermogenesis is the increase in energy expenditure associated with the digestion, absorption, and storage of food. It may be the invariant energy cost of converting food to metabolic fuels (15, 16), or it may be actively regulated in response to changing food intake (17, 18). We measured postprandial thermogenesis using indirect calorimetry and found that it increased by 14% with overfeeding (Table 2). This increase was more likely due to greater dietary intake (16) than to an adaptive response because the thermic response to a meal of fixed energy content (200 kcal, 0.8 MJ) was the same before and after overfeeding (11 ± 5 compared with 12 ± 7 kcal per meal), consistent with observations of other investigators (14). Furthermore, interindividual differences in postprandial thermogenesis did not correlate with fat gain (Fig. 1B), suggesting that this was not a significant factor in fat gain.

Physical activity thermogenesis can be subdivided into volitional exercise (sports and fitness-related activities) thermogenesis and what we characterize as nonexercise activity thermogenesis (NEAT). NEAT is the thermogenesis that accompanies physical activities other than volitional exercise, such as the activities of daily living, fidgeting, spontaneous muscle contraction, and maintaining posture when not reclined. The possibility that NEAT might mediate resistance to fat gain intrigued us because spontaneous physical activity (a component of NEAT) is a familial trait (19) that shows marked interindividual differences in its contribution to daily energy expenditure (19, 20) and is somewhat predictive of future weight gain (21). Also, nonresting energy expenditure (which includes NEAT) increases in adults subjected to a controlled 10% weight gain (22). Finally, in previous overfeeding studies (3), it has been possible to account for only ~30% of the calories that are “wasted” through increased energy expenditure. If NEAT accounts for the remaining 70%, then variable activation of NEAT in response to overeating could explain the wide variations in weight gain.

Measurement of overfeeding-induced changes in NEAT is formidable because of the complexity of differentiating NEAT from volitional exercise thermogenesis in free-living humans. We accomplished this differentiation by stringently maintaining volitional exercise at constant, low levels, and we confirmed compliance through questionnaires and direct measures of physical activity. Although we appreciated that volitional exercise might change in response to overeating, we viewed this as a behavioral rather than a physiological adaptation and so elected to eliminate it as a confounding variable. Because changes in exercise efficiency would affect physical activity thermogenesis (23), this variable was also measured. If the level and efficiency of volitional exercise remained constant over time, then changes in physical activity thermogenesis (NEAT plus volitional exercise) would represent changes in NEAT. Hence, we assessed physical activity thermogenesis before and after overfeeding by measuring total daily energy expenditure using doubly labeled water and subtracting from it the sum of basal and postprandial energy expenditure. These steps allowed us to assess whether changes in NEAT mediate resistance to fat gain with overfeeding.

NEAT proved to be the principal mediator of resistance to fat gain with overfeeding. The average increase in NEAT (336 kcal/day) accounted for two-thirds of the increase in daily energy expenditure (Table 2), and the range of change in NEAT in our volunteers was large (~98 to +692 kcal/day). However, most importantly, changes in NEAT directly predicted resistance to fat gain with overfeeding (Fig. 1C), and this predictive value was not influenced by starting weight (24).

Thus, activation of NEAT can explain the variability in fat gain with overeating. As humans overeat, those with effective activation of NEAT can dissipate the excess energy so that it is not available for storage as fat, whereas those with lesser degrees of NEAT activation will likely have greater fat gain and be predisposed to develop obesity. The maximum increase in NEAT that we detected (692 kcal/day, volunteer 5) could be accounted for by an increase in strolling-equivalent activity (25) by about 15

![Fig. 1.](image.png)  
Fig. 1. The relation of the change in (A) basal metabolic rate, (B) postprandial thermogenesis, and (C) activity thermogenesis with fat gain after overfeeding (27–33). Exercise levels and the thermic efficiency of exercise were unchanged with overfeeding, so that changes in activity thermogenesis represent changes in NEAT.

Table 2. The fate of the excess 1000 kcal/day consumed by 16 volunteers during 8 weeks of overfeeding. Data are expressed as kilocalories per day.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Standard deviation</th>
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</tr>
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<tr>
<td>Fat mass gain*</td>
<td>389</td>
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<tr>
<td>Fat-free mass gain*</td>
<td>43</td>
<td>22</td>
<td>15–78</td>
</tr>
<tr>
<td>Change in resting energy expenditure</td>
<td>79</td>
<td>126</td>
<td>−100–360</td>
</tr>
<tr>
<td>Change in thermic effect of food</td>
<td>137</td>
<td>83</td>
<td>28.2–256</td>
</tr>
<tr>
<td>Change in NEAT</td>
<td>328</td>
<td>256</td>
<td>−98.3–692</td>
</tr>
</tbody>
</table>

*Energy contents of tissues were calculated with published constants (3).
min/hour during waking hours. Of interest, the four lowest values for change in NEAT corresponded to the four female volunteers, although the relation between change in NEAT and fat gain was the same in males and females. A larger study will be needed to determine the significance of the preliminary gender differences noted here. Another limitation of our study is the small errors inherent in measuring energy expenditure and body composition in physiological studies. Because these errors are cumulative, they would be expected to weaken the association between the change in NEAT and the change in body fat. Thus, it is possible that we have underestimated the contribution of NEAT activation to the resistance to fat gain with overfeeding.

Finally, our results suggest that efforts to enhance NEAT activation, perhaps through behavioral cues, may be a fruitful approach to the prevention of obesity.

References and Notes

24. If total daily energy expenditure measured with doubly labeled water is assumed to equal weight maintenance requirements (rather than the measures of weight maintenance dietary intake), the relation between the increase in NEAT and the efficiency of energy storage (excess kilocalories stored/number of excess kilocalories provided) is almost identical to the relation we report in Fig. 1C (r = −0.80, P < 0.001, compared with r = −0.77, P < 0.001).
27. The 16 (12 males and 4 females) healthy volunteers were 25 to 36 years old. Volunteers were excluded if they used any medication at the time of the study or within 6 months of the study, exercised more than twice each week, smoked, used alcohol, were pregnant, had any history of chronic illness, or reported unstable body weight.
28. Volunteers were studied as outpatients for 10 weeks. Meals were prepared in the metabolic kitchen at the Mayo Clinic General Clinical Research Center (GCRC). All foods were weighed to within 1 g. For the first 2 weeks, volunteers were fed so as to establish the dietary intake necessary to maintain steady-state body weight. For the remaining 8 weeks, each volunteer received 1000 kcal in addition to weight maintenance requirements. The diet composition remained constant throughout the study at 40% carbohydrate, 40% fat, and 20% protein. Body weight was measured each morning under standardized conditions (with an empty bladder, without shoes, and wearing consistent, light clothing); these measures were made by GCRC personnel. Volunteers were instructed not to adopt new exercise practices and were questioned daily regarding activities. In addition, volunteers’ family and friends underwent structured interviews before and after feeding to determine compliance with exercise restrictions. During weeks 2 and 10, volunteers wore accelerometers (with disabled liquid crystal displays) (Caltrac; Muscle Dynamics, Torrance, CA) to measure the extent of free-living exercise-related activity. To ensure compliance with the feeding regimen, volunteers were instructed to eat all foods provided, and almost all meals were consumed under supervision at the GCRC. Plates were inspected for food and liquid remnants. When food items were eaten outside of the GCRC, preweighed food items were provided by the investigators, and empty food containers were inspected. On occasion, volunteers’ home garbage was checked. Family members, friends, and work colleagues of the volunteers were identified and contacted on several occasions throughout the study to ensure that all food was consumed as instructed. Informed consent was obtained after the nature and possible consequences of the study were explained.
29. Each volunteer was weighed daily with the same calibrated scale. Body mass was measured in duplicate with DXA after baseline feeding (end of week 2) and after completion of overfeeding (end of week 10). To ensure that our measures of body composition were reproducible and precise, we used the same DXA scanner throughout the study, (ii) we calibrated the DXA scanner before each measurement with tissue phantoms, and (iii) we calibrated the DXA scanner against international reference scans.
30. A human adipose tissue block with a lipid content of 282% by chemical analysis was found to be 249 g by DXA. A tissue block mass obtained from the mean DXA and isotope dilution revealed a strong correlation (r = 0.97, P < 0.0001). Finally, when a 600-g block of adipose tissue was placed on a volunteer with 22.8 g of body fat as assessed by DXA, 577 g of this block was detected as fat by DXA. This difference calculated for the test-retest difference for duplicate measurements was <2%.
31. BMR was measured on two consecutive mornings at 0630 in volunteers who had slept uninterrupted the previous nights in the GCRC. Volunteers were not moved before and after measurements. For each measurement, the calorimeter (Deltatrac; SensorMedics, Yorba Linda, CA) was calibrated with gases of known composition. Volunteers were awakened, had their head softly lightly clothed, and in thermal comfort (68° to 74°F) in a dimly lit, quiet room. Measurements were performed for 30 min during which time volunteers were not allowed to talk or move. The test-retest difference for duplicate measurements was <3%.
32. Postprandial thermogenesis was measured in consecutive days at the ends of weeks 2 and 10. On the first study day, volunteers were given a meal that provided one-third of their daily intake (40% carbohydrate, 40% fat, and 20% protein). Energy expenditure was measured with the indirect calorimeter for 15 of every 30 min (to prevent agitation) until values within 4 kcal/min/energy expenditure were recorded for two consecutive measurements. On the second day, volunteers were provided with a 200-kcal meal (40% carbohydrate, 40% fat, and 20% protein), and the same procedures were followed.
33. Changes in NEAT were measured by calculating activity-related thermogenesis before and after overfeeding. Activity-related thermogenesis was determined by measuring total energy expenditure, with doubly labeled water, and subtracting from it the sum of basal energy expenditure and postprandial energy expenditure. Subtraction of the effect of diet-induced thermogenesis before overfeeding from the value obtained after overfeeding represented the change in NEAT if two conditions were met: (i) the total amount of volitional exercise was unchanged and (ii) the thermic efficiency of exercise was unchanged. We determined that the amount of exercise did not change with overfeeding by using the test-retest difference for duplicate measurements (SD) 39 min. Daily postprandial energy expenditure was calculated on each measure-
34. We thank the volunteers, dietitians, food technicians, and nursing staff at the GCRC and A. Wright and K. U. C. for their help.
35. Changes in NEAT were measured by calculating activity-related thermogenesis before and after overfeeding. Activity-related thermogenesis was determined by measuring total energy expenditure, with doubly labeled water, and subtracting from it the sum of basal energy expenditure and postprandial energy expenditure. Subtraction of the effect of diet-induced thermogenesis before overfeeding from the value obtained after overfeeding represented the change in NEAT if two conditions were met: (i) the total amount of volitional exercise was unchanged and (ii) the thermic efficiency of exercise was unchanged. We determined that the amount of exercise did not change with overfeeding by using the test-retest difference for duplicate measurements (SD) 39 min. Daily postprandial energy expenditure was calculated on each measure-
36. We thank the volunteers, dietitians, food technicians, and nursing staff at the GCRC and A. Wright and K. U. C. for their help.
37. Recent progress in diet-induced thermogenesis and the thermic efficiency of exercise were unchanged with overfeeding, any change in activity-related thermogenesis after overfeeding represented the change in NEAT. Finally, to ensure that energy wastage did not occur through malabsorption, 3-day stool fat was measured before and after overfeeding. There was no significant increase in stool fat with overfeeding (25 ± 13 kcal/day compared with 38 ± 15 kcal/day).
38. We thank the volunteers, dietitians, food technicians, and nursing staff at the GCRC and A. Wright and K. U. C. for their help.

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