Energy Expenditure, Fat Oxidation, and Body Weight Regulation: A Study of Metabolic Adaptation to Long-Term Weight Change

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ABSTRACT

Relatively low rates of energy expenditure and fat oxidation predict body weight gain. Weight gain, in turn, is associated with increases in energy expenditure and fat oxidation that may oppose further weight change. In response to experimental weight gain induced by overfeeding, increases in energy expenditure and fat oxidation are overcompensatory, i.e. greater than predicted for the change in body composition. To determine whether such metabolic adaptation occurs in response to spontaneous long term weight change, we conducted a longitudinal study in which 24-h energy expenditure (24-EE) and 24-h respiratory quotient (24-RQ; i.e. fat to carbohydrate oxidation) were repeatedly measured in 102 Pima Indians at baseline and after a mean follow-up of 3.6 ± 2.7 yr, during which changes in body weight varied widely (−21 to +28 kg). We found that changes in 24-EE and 24-RQ in response to weight change were related to the amount of weight change, even after adjustment for body composition (partial $r = 0.23$ and $−0.30$, respectively; both $P < 0.05$). For a 15-kg weight gain, the increases in 24-EE (+544 Cal/day) and 24-h fat oxidation (+152 Cal/day) were 33 and 53 Cal/day greater than predicted from the cross-sectional relationship between both measures and body weight. Changes in 24-EE and 24-RQ varied substantially among individuals. Thus, on the average, spontaneous long term weight changes are accompanied by small metabolic adaptations in both energy expenditure and fat oxidation. The metabolic responses to weight changes are highly variable among individuals, however. (J Clin Endocrinol Metab 85: 1087–1094, 2000)

The prevalence of overweight and obesity has increased considerably in the United States in recent years, and it is estimated that some 22% of Americans are currently obese (1). To develop successful prevention and treatment strategies, it is important to understand the physiological mechanisms underlying the long term regulation of body weight.

Differences in energy metabolism may play a role in long term body weight regulation and the pathogenesis of human obesity (2–13). Several (2–7), but not all (8–10), prospective studies have shown that a relatively low energy expenditure (2–5) and a relatively high respiratory quotient, i.e. a low fat to carbohydrate oxidation rate (6, 7) predict body weight gain. Longitudinal studies, however, in which energy metabolism was assessed not only at baseline but also at follow-up, indicate that upon gaining weight, energy expenditure and fat oxidation increase (2, 6, 13). Metabolic propensity to obesity might thus depend not only on initial rates of energy expenditure and fat oxidation, but also on how these measures change in response to weight change (13).

Results from most overfeeding studies indicate that short term experimental weight gain is accompanied by an overcompensatory increase in energy expenditure, i.e. an increase in energy expenditure that is greater than predicted for the changes in body size and composition (14–22). Similarly, most underfeeding studies reveal that in the short term, intentional weight loss leads to a decrease in energy expenditure beyond predicted values (23–36). Such overcompensatory metabolic changes act to oppose further weight change and have thus been referred to as metabolic adaptation (13, 24, 37).

Although metabolic adaptation thus seems to occur in response to large perturbations in body weight over relatively short periods of time, it is unknown whether similar adaptive mechanisms also occur in response to spontaneous long term weight changes in free living conditions.

To examine this question, we analyzed data from an ongoing longitudinal study of the pathogenesis of obesity initiated in 1985 among the Pima Indians of Arizona, a population with a very high prevalence of obesity, in whom low rates of energy expenditure and fat oxidation predict body weight gain (2, 6). We present results from over 100 subjects in whom 24-h energy expenditure and 24-h substrate oxidation were repeatedly measured in a whole body respiratory chamber before and after an average follow-up of 3.6 yr during which changes in body weight varied widely. The aims of this study were 1) to test whether metabolic adaptation in 24-h energy expenditure and 24-h substrate oxidation occur in response to spontaneous long term weight change, 2) to quantify and explain the variability in these changes among individuals, and 3) to determine the relationship between changes in energy expenditure and substrate oxidation in response to weight gain and weight loss.

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Subjects and Methods

Subjects

Since 1985, Pima Indians have been admitted to the metabolic ward of the Clinical Diabetes and Nutrition Section of the NIH in Phoenix, Arizona, for an ongoing longitudinal study of the pathogenesis of obesity that includes the repeated assessment of 24-h energy expenditure and 24-h substrate oxidation in a whole body respiratory chamber. Subjects with diabetes mellitus and subjects who were not in energy balance (energy intake ±20% of expenditure during the stay in the chamber) or who had participated in studies involving diet, exercise, or any other interventions affecting body weight or energy metabolism, were excluded from the analysis. Among the 491 subjects meeting these criteria, 102 subjects had been studied on at least 2 occasions. In subjects studied more than twice, the visit with the greatest weight change was selected for follow-up. Among the 102 subjects, 31 subjects had lost weight and 71 had gained weight at follow-up. All subjects were between 18–50 yr of age at baseline and follow-up, healthy according to the NIH criteria for the metabolic syndrome (1), or had been diagnosed as diabetic. All subjects were free from cardiovascular disease and from any medications at baseline or follow-up (Table 1).

All subjects stayed on the metabolic ward for at least 3 days, where they were fed a weight-maintaining diet (50%, 30%, and 20% of daily calories provided as carbohydrate, fat, and protein, respectively) and abstained from strenuous physical activity before evaluation in the chamber. Glucose tolerance was assessed by a 75-g oral glucose tolerance test (38). The study protocol was approved by the Institutional Review Board of the NIDDK and by the Tribal Council of the Gila River Indian Community, and all subjects provided written informed consent before participation.

Body composition

Body composition was estimated by underwater weighing, with determination of residual lung volume by helium dilution (39), or by total body dual energy x-ray absorptiometry (DPX-L, Lunar Corp., Madison, WI) (40). Percent body fat, fat mass (FM), and fat-free mass (FFM) were calculated as previously described (41), and a conversion equation (42) was used to make measurements comparable between the two methods. Waist and thigh circumferences were measured at the umbilicus and the midpoint of the thigh, respectively, and the gluteal fold in the supine and standing positions, respectively, and the waist to thigh ratio (WTR) was calculated as an index of body fat distribution (43).

Respiratory chamber

The measurement of energy expenditure and substrate oxidation in the respiratory chamber has been described (44). The amount of calories calculated according to previous determinations to achieve energy balance (45). Meals were provided at 0800, 1130, and 1700 h, and an evening snack was given at 2000 h. The rate of energy expenditure was measured continuously, calculated for each 15-min interval of the 23 h in the chamber, and then extrapolated to 24 h (24-h energy expenditure, 24-EE). Spontaneous physical activity (SPA) was detected by radar sensors and expressed as the percentage of time over the 24-h period in which activity was detected (44). Carbon dioxide production (VCO2) and oxygen consumption (VO2) were calculated at 15-min intervals, summed for the 23 h in the chamber, and then extrapolated to 24 h. The 24-h respiratory quotient (24-RQ) was calculated as the ratio of 24-h VCO2 and 24-h VO2 and adjusted for the 24-h energy balance (24-h energy intake – 24-EE during the stay in the chamber) in a multiple regression analysis. Based upon 24-RQ, 24-EE, and 24-h urinary nitrogen excretion, the rates of 24-h fat, carbohydrate, and protein oxidation were determined as previously described (46).

Statistical analyses

Statistical analyses were performed using the procedures of the SAS Institute, Inc. (Cary, NC) (47). Results are given as the mean ± sd. Data from the entire group of 491 subjects were used to assess the cross-sectional relationships between 24-EE and 24-RQ vs. body weight (prediction line and its 95% confidence interval) and to calculate the adjusted values of 24-EE (FFM, FM, WTR, age, and sex) and 24-RQ (fat, age, and sex; multiple linear regression). Changes in anthropometric and metabolic parameters were assessed in the subset of 102 subjects with follow-up measurements. Changes (Δ) in 24-EE and 24-RQ were calculated as the difference between follow-up and baseline measurements for both the unadjusted and the adjusted values. Paired t tests were used to test whether measurements at follow-up were significantly different from those at baseline. Pearson correlation coefficients were calculated to assess the relation of the changes in unadjusted and adjusted 24-EE and 24-RQ to the change in body weight. Stepwise and general linear regression models were used to assess determinants of Δ 24-EE and Δ 24-RQ, the percentage of variance explained by these determinants (r2), and the residual variance that remains after adjustment (\(\sqrt{\text{MSE}}\) = root of the mean square error). The changes in 24-EE and 24-RQ predicted for a 15-kg weight loss or 15-kg weight gain were determined from the regression equation of the relationships between Δ 24-EE and Δ 24-RQ vs. Δ weight. These changes were superimposed onto the 95% confidence intervals of the prediction lines for the cross-sectional relationships between 24-EE and 24-RQ vs. body weight, as assessed in the entire study population of 491 subjects. The residuals of the relationships between Δ 24-EE and Δ 24-RQ vs. Δ weight were calculated using general linear regression models.

TABLE 1. Physical and metabolic characteristics of the entire study population and of the subset of 102 subjects with follow-up

<table>
<thead>
<tr>
<th></th>
<th>Entire population (n = 491)</th>
<th>Subjects with follow-up (n = 102)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Δ (min/max)</td>
</tr>
<tr>
<td>Females/males</td>
<td>183/308</td>
<td>32/70</td>
<td></td>
</tr>
<tr>
<td>NGT/IGT</td>
<td>365/128</td>
<td>91/11</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28.6 ± 8.7</td>
<td>26.9 ± 5.7</td>
<td>30.5 ± 6.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>93.1 ± 22.6</td>
<td>93.2 ± 23.9</td>
<td>97.7 ± 25.3</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>32 ± 9</td>
<td>32 ± 9</td>
<td>32 ± 8</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>35.5 ± 15.8</td>
<td>35.5 ± 16.5</td>
<td>37.4 ± 16.6</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>57.6 ± 11.6</td>
<td>57.7 ± 11.9</td>
<td>60.5 ± 12.0</td>
</tr>
<tr>
<td>Waist to thigh ratio</td>
<td>1.64 ± 0.16</td>
<td>1.66 ± 0.16</td>
<td>1.67 ± 0.16</td>
</tr>
<tr>
<td>24-h energy expenditure (Cal/day)</td>
<td>2316 ± 394</td>
<td>2237 ± 389</td>
<td>2394 ± 395</td>
</tr>
<tr>
<td>24-h energy intake (Cal/day)</td>
<td>2251 ± 333</td>
<td>2243 ± 363</td>
<td>2317 ± 383</td>
</tr>
<tr>
<td>24-h energy balance (Cal/day)</td>
<td>−85 ± 141</td>
<td>−84 ± 170</td>
<td>−47 ± 165</td>
</tr>
<tr>
<td>24-h respiratory quotient</td>
<td>0.852 ± 0.022</td>
<td>0.854 ± 0.023</td>
<td>0.853 ± 0.022</td>
</tr>
<tr>
<td>24-h fat oxidation (Cal/day)</td>
<td>920 ± 248</td>
<td>916 ± 287</td>
<td>951 ± 284</td>
</tr>
<tr>
<td>24-h carbohydrate oxidation (Cal/day)</td>
<td>1065 ± 215</td>
<td>1067 ± 256</td>
<td>1114 ± 212</td>
</tr>
</tbody>
</table>

Values are the Δ (min/max). At baseline, all measurements in the follow-up group were comparable to those in the entire population. The P values refer to the changes over time (determined by paired t-test). NGT/IGT, Normal/impaired glucose tolerance (33).
Results

The anthropometric and metabolic characteristics of the entire study population and of the subset of individuals with follow-up studies are summarized in Table 1. The baseline anthropometric and metabolic characteristics of the 102 subjects with repeated measurements of energy metabolism were similar to those of the entire study population. The follow-up duration ranged from 0.6–11.2 yr, averaging 3.6 ± 2.7 yr. During this time, body weight changes varied widely (ranging from −21 to +28 kg; Table 1).

Cross-sectional analysis (n = 491)

In the entire population of 491 subjects, 24-EE was positively related to body weight (r = 0.81; P < 0.0001; Fig. 1C), whereas 24-RQ was negatively related to body weight (r = −0.22; P < 0.0001; Fig. 2C).

Longitudinal analysis (n = 102)

Changes in 24-h energy expenditure. There was a positive linear correlation between the change in 24-h energy expenditure (Δ24-EE) and the change in body weight (Δ weight), but at any given Δ weight there was considerable interindividual variability in Δ24-EE (σ, 192 Cal/day; Fig. 1A). The correlation between Δ24-EE and Δ weight remained significant when baseline and follow-up 24-EE were adjusted for FFM, FM, WTR, age, and sex (Fig. 1B). The Δ SPA measured in the chamber was not related to Δ weight (r = 0.01; P = NS), and the correlation between Δ24-EE and Δ weight remained significant when baseline and follow-up 24-EE was additionally adjusted for SPA (partial r = 0.23; P < 0.05). When the changes in 24-EE predicted for a 15-kg weight loss and a 15-kg weight gain were superimposed onto the cross-sectional relationship between 24-EE and body weight as assessed in the entire population of 491 subjects, 24-EE fell below the 95% confidence interval after weight loss and above the 95% confidence interval after weight gain (Fig. 1C). For these weight changes, the calculated change in 24-EE (±244 Cal/day) was 16% (33 Cal/day) greater than that predicted from the cross-sectional relationship between 24-EE and body weight (±211 Cal/day; Fig. 1C).

The Δ weight alone explained 58% of the variability in Δ24-EE (r² = 0.58). In a multiple regression analysis, the ΔFFM, ΔFM, ΔWTR, and ΔSPA were significant independent determinants of Δ24-EE: Δ24-EE (Cal/day) = −25 + 14.9 ΔFFM (kg) + 16.5 ΔFM (kg) + 22.2 ΔWTR (decimal) + 9.7 ΔSPA (%). Together, these factors explained 63% of the variability in Δ24-EE, reducing the variance from 192 to 118 Cal/day (MSE). Sex, age, glucose tolerance status (normal or impaired), initial body weight, and follow-up duration were not significant determinants of Δ24-EE.

Changes in 24-h respiratory quotient and substrate oxidation. There was a negative linear correlation between Δ24-RQ and Δ weight, but for any given Δ weight there was considerable interindividual variability in Δ24-RQ (σp, 0.030; Fig. 2A). The correlation between Δ24-RQ and Δ weight remained significant when baseline and follow-up 24-RQ were adjusted for percent body fat, age, and sex in addition to energy balance in the chamber (Fig. 2B). When the changes in 24-RQ predicted for a 15-kg weight loss and a 15-kg weight gain were superimposed onto the cross-sectional relationship between 24-RQ and body weight, 24-RQ fell above the 95% confidence interval after weight loss and below the 95% confidence interval after weight gain (Fig. 2C). For this weight change, the calculated change in fat oxidation (±152 Cal/day) was 54% (53 Cal/day) greater than predicted from the cross-
The Δ weight alone explained only 9% of the variance in Δ 24-RQ ($r^2 = 0.09$). In a multiple regression analysis, the only additional independent determinant of Δ 24-RQ was age at baseline, explaining another 3% of the variance: Δ 24-RQ = −0.023 − 0.001 Δ weight (kg) + 0.001 age (yr) [residual variance ($\sqrt{MSE}$), 0.029]. Changes in percent body fat ($P = 0.09$) or WTR ($P = 0.13$) were not significant independent determinants of Δ 24-RQ, nor was sex, age, glucose tolerance status, initial body weight, or follow-up duration.

**Fig. 2.** A, Relationship between changes in 24-RQ, adjusted for energy balance, and Δ weight over 3.6 ± 2.7 yr in 102 nondiabetic Pima Indians. B, Relationship between Δ 24-RQ and Δ weight after adjustment of 24-RQ for percent body fat, age, and sex in addition to energy balance. C, Predicted changes in 24-RQ attributable to a 15-kg weight loss and a 15-kg weight gain (arrows) superimposed onto the cross-sectional relationship between 24-RQ and body weight as assessed in 491 nondiabetic Pima Indians (prediction line with its upper and lower 95% confidence intervals is shown).

The Δ weight alone explained only 9% of the variance in Δ 24-RQ ($r^2 = 0.09$). In a multiple regression analysis, the only additional independent determinant of Δ 24-RQ was age at baseline, explaining another 3% of the variance: Δ 24-RQ = −0.023 − 0.001 Δ weight (kg) + 0.001 age (yr) [residual variance ($\sqrt{MSE}$), 0.029]. Changes in percent body fat ($P = 0.09$) or WTR ($P = 0.13$) were not significant independent determinants of Δ 24-RQ, nor was sex, age, glucose tolerance status, initial body weight, or follow-up duration.

**Fig. 3.** Relationship between residual Δ 24-RQ and residual Δ 24-EE in response to either weight gain (**upper panel;** $n = 71$) or weight loss (**lower panel;** $n = 31$) in 102 nondiabetic Pima Indians in whom body weight changed widely over 3.6 ± 2.7 yr.
Discussion

In the present longitudinal study we examined the changes in 24-h energy expenditure and 24-h substrate oxidation associated with spontaneous long term weight changes in more than 100 Pima Indians who spent 24-h in a respiratory chamber at baseline and after a mean follow-up of 3.6 yr, during which changes in body weight varied widely.

The results indicate that metabolic adaptation, i.e. changes in energy expenditure and substrate oxidation greater than predicted for the change in body size and composition, can occur in response to spontaneous long term weight changes. On the average, the metabolic changes were only slightly greater than predicted, but varied substantially among individuals. Finally, we found that in response to weight gain, adaptations in energy expenditure and substrate oxidation were related to one another, such that subjects with the most pronounced metabolic adaptation in energy expenditure also had the most pronounced metabolic adaptation in fat oxidation and vice versa. This was not the case for weight loss.

Most previous intervention studies have demonstrated metabolic adaptation in response to experimental short term weight change induced by controlled over- and underfeeding regimens (14–36). Whether similar overcompensatory changes in energy expenditure and fat oxidation occur in the natural history of weight changes has been a matter of contention (9–13, 16, 26).

The present study demonstrates, for the first time, that metabolic adaptation can occur in response to spontaneous long term weight changes, but also reveals that, on the average, these overcompensatory changes are small. We estimate that a 15-kg weight change is accompanied by a change in 24-h energy expenditure of 244 Cal/day, which is only 33 Cal/day greater than predicted from the cross-sectional relationship between 24-h energy expenditure and body weight (211 Cal/day). The change in 24-h fat oxidation after a 15-kg weight change was 53 Cal/day greater than predicted from the cross-sectional data. In practical terms, these adaptations translate into the caloric content of approximately one half of an apple, one fifth of a bagel, or one tenth of a cheeseburger (for the adaptation in 24-h energy expenditure) or the fat content of two teaspoons of peanut butter or seven potato chips (for the metabolic adaptation in 24-h fat oxidation), respectively.

These data indicate that in the long term, the defense mechanisms of the body to resist weight gain by an overcompensatory increase in energy expenditure and/or fat oxidation are relatively weak and easy to offset by small changes in food intake. The results also indicate that even a large decrease in body weight over several years is, on the average, not accompanied by a profound slowing of energy metabolism, as occasionally implied to explain the high rate of weight recidivism in the medical treatment of obesity. However, several aspects need to be considered in this respect.

First, it has been demonstrated that even small differences in energy expenditure and/or substrate oxidation that may appear trivial on a daily basis can have an important impact on body weight over the long term (2, 6). In a previous prospective study (2), we found that a difference in energy expenditure of only 70 Cal/day was associated with marked differences in subsequent weight gain.

Second, the present study was observational in design, which has both advantages and disadvantages. On the one hand, we have no information on the exact causes of the weight changes. In some individuals, weight loss might have been secondary to illness, although this is unlikely because subjects in our studies typically remain in close contact with the research unit and receive a comprehensive medical examination before each admission. An advantage of the observational design, on the other hand, is that it allows us to examine the metabolic responses to spontaneous long term weight changes that probably more closely resemble the typical pattern of weight change under free living conditions than imposed by over- and underfeeding regimens. The fact that the magnitude of metabolic adaptation in response to such gradual weight change was small, on the average, agrees with cross-sectional findings indicating that energy expenditure is only marginally reduced in formerly obese individuals who had returned to a normal body weight and had successfully maintained the weight loss over months or years (postobese individuals) (50). Some previous intervention studies suggest that the suppression in energy expenditure in response to weight loss might be larger shortly after a more rapid decrease in body weight (26, 27, 29, 31, 36).

It is also important to point out that energy expenditure in the present study was measured in the restricted environment of a respiratory chamber, which significantly reduces physical activity. Although nonexercise activity thermogenesis, of which spontaneous physical activity is a component, has recently been suggested to play an important role in the adaptation to overfeeding (21), our findings do not suggest a major role of spontaneous physical activity (i.e. fidgeting) in the metabolic response to long term weight change. To what extent changes in voluntary physical activities such as exercise habits contribute to the overall metabolic responses to long term weight change remains unknown. Our study also provides no information on the role of spontaneous adaptations in energy intake. Because an increase in body weight of 15 kg resulted in an increase in energy expenditure of about 200–250 Cal/day, a similar increase in energy intake must have occurred to maintain the higher body weight. Thus, as with the metabolic adaptation in energy expenditure, small differences in the adaptation in energy intake may play an important role in determining whether body weight remains stable or continues to increase.

Although the adaptations in energy metabolism were small, on the average, the present study reveals that the differences in subsequent weight gain. Thus, weight gain/loss is not universally accompanied by small adaptive increases/decreases in energy expenditure and/or fat oxidation. Rather, some individuals will experience relatively large overcompensatory responses, whereas others will have subnormal responses. Such individual variability in metabolic responses has also been found in response to experimental over- and underfeeding and has been used to explain why the amount of weight gained or lost under
standardized dietary regimens can differ substantially among individuals (14, 19, 22, 26). The large number of subjects in the present study allowed us to quantify the interindividual variability in metabolic responses to weight changes and to search for possible underlying determinants. We found that the change in 24-h energy expenditure was explained not only by the changes in FFM and FM, but also independently by the changes in body fat distribution and spontaneous physical activity. The only additional determinant of the change in 24-h respiratory quotient was age at baseline. The effect of these additional factors was small, however, and as much as 37% of the variability in Δ 24-h energy expenditure and 89% of the variability in Δ 24-h respiratory quotient remained unexplained. As only a small part of this variability can be attributed to the variability of the method (2, 6, 44), other factors must be involved. These may include, for example, changes in plasma thyroid or sex hormone concentrations (49), autonomic nervous system activity (51, 52), mitochondrial uncoupling activity (53), plasma insulin and free fatty acid concentrations, and glucose tolerance (54), each of which was found to be related to energy expenditure and/or substrate oxidation in cross-sectional studies. Moreover, there is strong evidence from overfeeding studies in identical twins that the metabolic responses to weight changes are in part genetically determined (55, 56).

Another interesting observation in the present study was that in response to weight gain, the changes in 24-h energy expenditure and 24-h substrate oxidation were related to one another, in that individuals with the most pronounced adaptation in energy expenditure also tended to have the most pronounced adaptation in fat oxidation and vice versa. Interestingly, this was not the case in response to weight loss, where adaptations in energy expenditure and substrate oxidation were unrelated.

The above findings may have important implications for our understanding of the role of energy metabolism in the long term regulation of body weight and the pathogenesis of human obesity. To illustrate this, we have developed a schematic model that integrates previous cross-sectional and prospective findings with those from the present longitudinal study (Fig. 4).

Cross-sectionally, energy expenditure and the rate of fat to carbohydrate oxidation increase with increasing body size (prediction line), but at any given body size, both measures vary considerably among individuals (44, 51, 57). Several prospective studies revealed the relative importance of this variation, in that relatively low rates of energy expenditure (2–5) and/or fat oxidation (6, 7) predispose individuals to weight gain (arrows 1A and 1B in Fig. 4). Our present longitudinal data indicate that upon gaining weight, the initially low rates of energy expenditure and fat oxidation tend to normalize, on the average, but as with the cross-sectional relationship, there is substantial interindividual variability in these responses. Accordingly, the metabolic drive to weight gain may soon diminish in some individuals, thereby limiting the amount of weight gain (metabolic adaptation; arrow 1A), whereas it may be sustained in others, who will thus be predisposed to gain further weight (arrow 1B). Conversely, individuals with relatively high rates of energy expenditure and/or fat oxidation are predisposed to spontaneously lose weight, but the amount of weight loss will depend upon the occurrence (arrow 2A) or not (arrow 2B) of metabolic adaptation. Of note, these considerations apply to spontaneous long term weight changes. If, for instance, an obese individual decides to intentionally lose weight, his or her initial energy expenditure and/or fat oxidation may fall below rather than above the normal range.

Further studies are needed to confirm the role of low

![Fig. 4. Schematic model integrating cross-sectional, prospective, and longitudinal findings to illustrate the potential role of energy expenditure and substrate oxidation in the long term regulation of body weight. Arrows 1A/2A, Pronounced metabolic adaptation→ quick decrease in the metabolic drive→ small weight change; arrows 1B/2B, no metabolic adaptation→ sustained metabolic drive→ large weight change (detailed explanation provided in Discussion).](image-url)
energy expenditure and fat oxidation as predictors of weight gain and to formally test the effect of metabolic adaptation on further weight change. It will also be important to examine the role of adaptation in energy and substrate intake to weight change. These are probably complex and could include changes in the perception of hunger and satiation as well as in caloric intake and food preferences.

In summary, the results of this longitudinal study indicate that the changes in 24-h energy expenditure and 24-h respiratory quotient (i.e. in substrate oxidation) associated with long term weight changes 1) are greater than those predicted for the change in body size and composition, 2) vary substantially among individuals, and 3) are related to one another in response to weight gain.

We conclude that metabolic adaptation can occur not only in response to experimental short term perturbations in body weight, but also in response to spontaneous long term weight changes. These responses, albeit small on the average, vary substantially among individuals and may thus play a role in the long term regulation of body weight and the pathogenesis of human obesity.

Acknowledgments

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