Metabolism and nutritional adaptation to altered intakes of energy substrates\textsuperscript{1,2}

W Philip T James, Geraldine McNeill, and Ann Ralph

ABSTRACT Adaptive changes in energy expenditure to changes in energy intake are far less than previously believed once changes in body weight and physical activity are taken into account. Alterations in metabolic efficiency of $\pm 10\%$ in total energy expenditure are the limits of what can normally be expected on prolonged under- or overfeeding. The supposed twofold variation in energy requirements of adults is based on measurements of food intake, which, despite involving weighed intakes over a week, cannot be considered realistic. Subtle differences in the energetic responses to fat, protein, and carbohydrate signify the different effective energetic contribution of isenergetic substrates and may account for the propensity to obesity in individuals and societies on a high-fat diet. \textit{Am J Clin Nutr} 1990;51:264–9.

KEY WORDS Nutritional adaptation, overfeeding, underfeeding

Introduction

Adaptations to changes in total energy intake are usefully considered separately from those in response to different energy substrates. It is becoming clear that total energy expenditure is almost always determined by the tissue demand for ATP in response to biological or mechanical work, but the substrates used for providing this energy can depend on substrate intake and on hormonal and other factors. The routing of metabolism then may explain why substrates that are isenergetic in terms of bomb calorimetry have different effects on energy expenditure.

Substantial flexibility in energy expenditure has seemed plausible since Widdowson more than 50 y ago obtained dietary data (1, 2) that highlighted interindividual differences in the energy intake of children and adults. She noted that in any group it was usual to find some individuals eating twice the energy intake of others of similar age, sex, and size. The observation of Sims et al (3) that prisoners were apparently able to withstand prolonged overfeeding with only modest weight gains, and the account of Miller et al (4) of a field study where rapid increases in energy expenditure were reported within 2 wk of overfeeding, all seemed to point to a substantial adaptive capacity in energy expenditure in man. Miller claimed that the thermogenic adaptation to changes in energy intake did not affect the metabolism of the body under basal conditions and that the key component was the interaction between physical activity and diet. A synergism of effect was proposed that could only be documented fully by accurate studies conducted on a 24-h basis during which subjects maintained reasonable activity levels. At this time a reduction in metabolic rates in response to semistarvation was also well accepted so differences in the metabolic flexibility between lean and obese subjects were then sought in the hope that an identifiable mechanism for reduced adaptability would be found in obese subjects.

The proposition of adaptability in energy metabolism has also assumed considerable political significance for development and other aid projects in the Third World countries because Sukhatme and Narain (5) proposed that costless adaptation could occur and that adults had the ability to reduce energy requirements by up to 30% without altering their weight or physical activity and therefore without detriment to health or productive capacity. This has obvious attractions for donor countries because food aid or support for rural development projects geared to agricultural production could then be reduced substantially. The papers of Sims et al, Miller et al, and Sukhatme and Narain (3–5) suggest that the differences in intake between people as documented by standard techniques imply that there are differences in energy expenditure. These could then reflect adaptive responses to the prevailing differences in intake set, for example, by social factors. Alternatively the differences in energy expenditure could reflect sustained differences in metabolic efficiency of an innately rather than an adaptive character.

Interindividual differences in energy intake and expenditure

Reinvestigating the basis for the difference between individuals with a high or low energy intake supports Widdowson’s observations (1, 2) but not the standard interpretation of these data. It is relatively easy to find a wide range in energy intake between individuals when intake is measured by careful monitoring of the weight of all food and drink eaten over a single week. When intakes measured for 1 wk are remeasured, then correlations in energy intake are maintained for a substantial period between the two measurements (6), implying consistency in each individual’s measurements. When, however, we

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TABLE 1
A reanalysis of the energy expenditure of young adults assessed as
individuals who ate large and small amounts

<table>
<thead>
<tr>
<th>Study</th>
<th>Rose and Williams (8)</th>
<th>Morgan et al (9)</th>
<th>McNeill et al (7)</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject number</td>
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<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.3</td>
<td>81.4</td>
<td>67.9</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>—</td>
<td>22.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Intake (MJ/d)</td>
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<td>8.5</td>
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<tr>
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<td>83.7</td>
<td>125.5</td>
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<tr>
<td>BMR (MJ/d)</td>
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<td>6.8</td>
<td>7.2</td>
</tr>
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<td>Survival requirement</td>
<td>1.2 × BMR (MJ/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>(MJ/d)*</td>
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<td>—</td>
</tr>
<tr>
<td></td>
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<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Large eaters</td>
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<tr>
<td>Subject number</td>
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<td>8</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Body fat (%)</td>
<td>—</td>
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<tr>
<td>BMR (MJ/d)</td>
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<td>Survival requirement</td>
<td>1.2 × BMR (MJ/d)</td>
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<td></td>
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<td>10.6</td>
<td>8.9</td>
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</tbody>
</table>

* Measured for 24 h in a whole-body calorimeter with a standardized regime of physical activity.

studied five individuals who ate large amounts and five who ate small amounts, under standardized physical-activity and food-intake conditions in a calorimeter chamber for periods of 24 h, there were no appreciable differences between the two groups in either their sleeping metabolic rates or in their 24-h energy expenditure. Basal metabolic rate (BMR) measured with a ventilated hood also showed no significant differences between the groups (7). Because the subjects followed a fixed pattern of physical activity in the calorimeter, it is also evident that the metabolic cost of physical activity must be very similar in the large and small eaters.

These findings at first seem very anomalous but in practice are little different from those noted by earlier workers. Short-term measurements using Douglas bags and other simple equipment were made by Rose and Williams (8) and more recently by Morgan et al (9), all of whom also looked for metabolic differences between small and large eaters. Table 1 draws all three studies together. In the two earlier studies and in the BMR measurements in the McNeill study, the subjects were studied on their habitual intakes so no artificial constraints were imposed. In our 24-h energy-expenditure measurements, however, both the large and small eaters were fed for 3 d at 1.5 times their measured BMRs. In theory the 24-h energy expenditure could have been influenced by the similar energy intake of the two groups, although other studies cited below suggest that 24-h energy expenditure in calorimeter chambers is not markedly responsive to changes in energy intake. If the measurements of these three studies are accepted, then to try to explain the intake data, one must presume that the large eaters are very active and the small eaters extremely inactive in everyday life. Activity diaries in the McNeill study suggest that only 20% of the difference in energy intake between the two groups could be accounted for by higher physical activity in the large eaters, leaving a large part of the apparent difference in energy requirements unexplained. The data clearly show that in all three groups there appears to be a major problem with the low intake data. The data on low food intakes must be wrong because the intake is sometimes less than the measured BMR and therefore does not allow for the known energy requirements of even modest physical activity, let alone the documented activity. If the survival requirement, eg, for resting in bed but maintaining energy balance, is taken at only 1.2 times the BMR, then the studies show intakes for the groups of small eaters (Table 1) to be often inadequate for survival. Furthermore, the supposed intake of energy in the large-eaters group varies from 1.7 times the BMR (which is realistic) to 2.5, which would imply extraordinary heavy laboring in subjects classified as medical students! These intake data must therefore be very suspect. Thus one should not infer from intake data that individuals differ widely in their energy requirements or metabolic efficiency.

Extensive studies of adult BMRs show that once an estimate has been made of the lean body mass of individuals, then the interindividual range of BMRs is very small, ie, 6–8% (10), and similar observations apply to 24-h measurements under standardized conditions (11). Recent studies by McNeill (unpublished observations, 1989) suggest that 90% of the variance in 24-h energy expenditure in 33 women aged 20–72 y and weighing 41–170 kg can be accounted for by differences in body weight alone (Fig 1). If there were appreciable intradiurnal variations in energy expenditure, then a greater range would be expected. These observations cast further doubt on the likelihood of finding large interindividual differences in 24-h energy expenditure apart from those explained by differences in body weight, body composition, and physical activity.

**Synergism between dietary and exercise thermogenesis**

Segal et al (12) monitored the short-term response to food in lean and obese men under conditions of rest and exercise. A
synergism was observed in the lean but not in the obese men. However, although the effect was claimed to be significant in the lean, it was not quantified and was certainly very small. In an earlier study on men of different body weights (13), the synergism was also found to be small and could amount at most to perhaps 420 kJ/d in the lean individuals. Thus under conditions of energy balance, synergism between exercise and diet is not a substantial portion of energy expenditure so there is only a very small component that could adapt under conditions of semistarvation.

Short-term fluctuations in energy expenditure

If Sukhatme’s hypothesis is to be sustained, then either there must be immediate energetic responses to altered energy intakes or a more sustained decrease in metabolic efficiency after a prolonged reduction in food intake. The limited short-term changes in energy expenditure in response to altered energy intakes was clearly demonstrated by Dauncey (14), who found that the 24-h energy expenditure response to a 50% increase or decrease in energy intake amounted to only ~10–20% of the change in intake, ie, about a 6–10% change in total energy expenditure. Similarly, De Boer (JO De Boer, unpublished observations, 1985) observed only small fluctuations in energy output when volunteers were given 100% or 50% of their normal energy intake on alternating days. Slower spontaneous changes in energy expenditure are excluded by our finding that the 24-h energy expenditure of subjects is remarkably constant when subjects are studied days, weeks, or even months later under standardized conditions. Thus a rapid daily costless adjustment in energy output of up to 30% without a change in physical activity or weight loss is not supported by any physiological evidence.

Prolonged responses to semistarvation

The classic studies on the extent and basis of adaptation to semistarvation were those conducted on young volunteers who had their food intakes severely restricted for 6 mo in the Minnesota experiment (15). These are summarized in Table 2. Energy expenditure was taken to be equal to intake because this is precisely controlled and weight was steady under both conditions of measurement. Most of the Minnesota data are taken from table 181 with values for body fat taken from table 457. Basal metabolic rates were measured, the specific dynamic action was estimated to be 10% of the intake, and the residual energy expenditure was calculated as physical activity by subtracting the BMR and specific dynamic action figures from the total intake figure and then adding 0.42 MJ/d to allow for the small continuing weight loss. Although there can be a profound decrease in BMR amounting to 45%, only 15% of this can be explained by a change in metabolic efficiency, the remaining decrease depending on weight loss. Lean tissue was lost in parallel with the decrease in body fat. In practice the decrease in BMR begins after ~4 d of semistarvation even without any appreciable loss of nitrogen (16) and reaches the full 15% drop within 2–3 wk. This implies that the adaptive metabolic response in BMR is early and that the later response depends on tissue depletion. If it is assumed that Keys’ volunteers were in energy balance in the last 4 wk of the 6-mo semistarvation period (as body weight decreased by on average 22 g/d over this period), then one can assume that the rate of energy expenditure was only ~420 kJ/d above the intake which had decreased by 7.9 MJ or 55%. Keys et al did not measure the dietary induced component of energy expenditure nor the metabolic cost of exercise. They noted, however, that there was a profound decrease in spontaneous physical activity of the subjects. By assuming energy equilibrium at the beginning of the study and noting the decrease in BMR from 6.7 MJ/d to 4.0 MJ/d it is evident that the combination of dietary induced thermogenesis and physical activity together accounted for a decrease of 5.3 MJ/d during the adaptive response. Table 2 shows that 54% of the adaptive response in energy expenditure was accounted for by a reduced physical activity and 35% by the decrease in BMR.

A number of studies have shown that the response to food is little affected by semistarvation if this is considered as the caloric response to a standard meal under basal resting conditions. After semistarvation little change is seen in the dietary induced response under resting conditions of obese women. This implies that in the Keys study changes in physical activity or its cost must have been the principal non-BMR change. Recent studies also confirm that prolonged semistarvation has only modest effects on metabolic efficiency (17–19). Overweight adults were semistarved for 8 wk and monitored for periods of 24 h in a whole-body calorimeter to test this possibility (17). A decline in the component of energy expenditure that included sedentary activities and dietary induced thermogenesis occurred with a decrease from 2.6 MJ on the first day of semistarvation to 2.3 MJ after 8 wk. This decrement amounts to only 11%, ie, very little more than the 8% decrease in sleeping metabolic rate. The net energy cost of bicycling also decreased from 9.6 kJ/m to 8.8 kJ/m, ie, ~7%, and some of this decline was due to the decrease in body weight. Thus there is little evidence for considering a dramatic change in metabolic efficiency associated with either food or physical activity as an important adaptive component.

Two other studies (18, 19) from Jequier’s group support these findings. Bessard et al (18) measured the 24-h energy expenditure of five obese women after an 11-wk period of hypocaloric feeding. The daily energy expenditure decreased from 9.2 MJ/d to 8.4 MJ/d in circumstances where the women were allowed to move spontaneously about the chamber. About 64%
of the decline in expenditure was accounted for by a decrease in the BMR, and formal studies of postprandial thermogenesis showed only a very small reduction on weight loss. In a later study on a similar protocol, Ravussin et al (19) found that the resting metabolic rate was unchanged after 11–16 wk of hypocaloric feeding provided an allowance was made for the decrease in fat-free mass that accounted for about half of the decrease in 24-h energy expenditure. A decreased thermic effect of food was noted but the decrease was in proportion to the decrease in the amount of energy being fed. Once a further allowance was made for the lower cost of exercise after weight loss, there seemed little need to involve any additional adaptive mechanisms. Thus in these studies on obese subjects, conducted for about one-third to one-half the time taken in Keys’ prolonged program of semistarvation of volunteers, there was not even an appreciable decrease in the BMR once allowance was made for changes in lean body mass. The Swiss subjects were studied as outpatients where dietary control is difficult to maintain, and they showed a lower weight loss than expected from the differences between the assumed energy expenditure and the purported dietary intakes. In our own studies on obese subjects, there is a decrease in BMR with selective carbohydrate underfeeding and this is reversible with levodopa, which serves as a catecholaminergic substrate and stimulus (16). It is conceivable that there is little or no metabolic efficiency change in obese subjects but profound changes in lean individuals. None of our calorimetry data on lean subjects support this idea (20) and, as noted earlier, the synergism between exercise thermogenesis and postprandial thermogenesis is unimpressive even in lean individuals. On this basis we conclude that the profound decrease in energy expenditure in Keys study depended primarily on the decrease in BMR and the decrease in overt physical activity, the latter being estimated to account for 57% of the total decline in energy expenditure.

Much more prolonged semistarvation or prolonged underfeeding from childhood could, however, modify metabolic efficiency and basal metabolism. Thus the BMRs of Indians tend to be ~10% below those predicted from values measured in Northern Europeans, which McNeill et al (21) and Shetty et al (22) ascribed to body compositional differences arising from chronic undernutrition in early childhood as well as a small reduction in BMR for climatic reasons.

Adaptations to overfeeding

The ability to adapt to overfeeding was considered substantial ever since Neumann (23) claimed that he could sustain his weight on very different intakes maintained over periods of several months. Gulick (24) concurred with this, noting that her own daily food intakes, measured methodically day by day for more than a year, could vary widely with little or no effect on body weight. These conclusions seemed to substantiate Miller’s later short-term experiments, but inspection of the original data shows that body weights did in fact vary in a predictable manner (25). Forbes (26) recalculated the data and showed that in practice the shifts in weight were consistent with a wide range of other studies, which suggested that on overfeeding > 70% of any excess energy is stored as a combination of fat and lean tissue. In weight terms early overfeeding seems to be associated with ~38% of the weight increase being laid down as lean tissue whereas in established obesity the average proportion of the excess weight ascribable to lean tissue decreases to 29%. There is therefore an increase in the excess energy required to deposit a given amount of weight with its higher fat content in obese individuals. There may, however, be differences in the intrinsic individual response to overfeeding between obesity-prone and lean individuals. Those prone to obesity may have a smaller increment in lean tissue than that observed in subjects of normal body composition when they are deliberately overfed.

These studies of weight changes on overfeeding are only indirect indices of changes in energy expenditure because it is necessary to make some assumptions about the energy stored. Direct measurements of energy output over periods of 24 h in calorimeters have been made in the last few years, and all fail to demonstrate any great flexibility in metabolic rates on overfeeding. Figure 2 summarizes the results of published and unpublished data that show that the increase in energy expenditure is modest and rarely amounts to > 15% of the original energy expenditure of the subjects. This increase includes the cost of continuing energy deposition because none of the studies were sufficiently prolonged to allow energy balance to be achieved once more. There is no suggestion that those with low rates of energy expenditure have a different response, and the period for which the overfeeding continues does not seem to be very important. Only when young men are force-fed by on average 11.59 MJ/d (6.3 MJ carbohydrate in excess of their previous 24-h expenditure) for 7 consecutive days does the energy expenditure increase by ~40%, but even this amounts to a modest 33% of the excess carbohydrate ingested (30).

In separate studies by the Sims group, Goldman et al (31) found that young volunteers increased their resting and postprandial metabolic rate when tested after 3 wk of overfeeding, but these responses are no different from the values observed on overfeeding for only a few days. These measurements were made under conditions of rest. However studies deliberately designed to test the interaction of exercise with overfeeding and involving overfeeding with selective carbohydrate (32), fat (29), or a mixed diet (33) show that any synergism between the exercise and dietary excess is so modest as to be difficult to discriminate even with very accurate whole-body calorimetry conducted under meticulously controlled conditions. Ravussin et al (33) studied volunteers during a 9-d overfeeding period on a mixed diet providing an extra 60% energy. A third of the increased expenditure was accounted for as a rise in BMR in line with the increase in lean tissue mass, and a further 29% was simply the proportional increase ascribable to the biochemical processing of the extra food. The remaining third was related to the energy cost of moving the extra 3.2 kg of weight gained during the overfeeding period during periods of weight-bearing physical activity.

None of these calorimetric studies on overfeeding were conducted for > 30 d, and the majority of overfeeding studies lasted only 1–2 wk. Nevertheless the effects after 1 wk amount to 89% of the effect after a second week of overfeeding, and it seems somewhat unlikely that a slow progressive amplification of metabolic rates occurred after 1–2 mo.

The original modelling system developed by Payne and Dugdale (34) suggests that equilibration to a maintained change in intake takes 2–3 y to achieve and depends on both the change in BMR, which relates to the accumulation of lean tissue, and on the changed cost of physical activity in heavier
people. None of the experimental results conflict with this model so it would seem that an adaptive process that involves, for example, a genuine change in metabolic processing is not necessary to explain the readjustments in energy balance. If semistarvation leads to a 15% decrease in BMR/kg lean tissue, then this is an early event that saves perhaps 10% of total daily energy expenditure. The overall effect of overfeeding amounts to a similar increase, but even this increase seems to reflect in part the processes of substrate storage. Thus the adaptive capacity of adult man seems to amount to ±10% of total energy expenditure under normal circumstances.

**Substrates dependent on changes in energy expenditure**

It has long been known that the ingestion of different substrates will increase energy expenditure to various degrees. Thus with single meals there is a much greater postprandial response to protein than to carbohydrate (35).

The effect of fat is less easy to document because it is so slowly absorbed through the lymphatics. Thus the oxidative response as assessed by feeding labeled fat and monitoring the labeling of expired carbon dioxide only begins at ~4 h and takes 6–10 h to induce maximum labeling (MEJ Lean, unpublished observation, 1986). The delay in the expired carbon dioxide labeling because of the preliminary labeling of the body bicarbonate pool will have only a modest effect on these observations. It is not surprising therefore that the immediate metabolic response to a meal is largely determined by the amount of carbohydrate and protein ingested (36). In more prolonged 24-h calorimetry studies Hurni et al (37) showed that when accurate measurements can be made, eg, during sleep, then a diet rich in carbohydrate and containing only 2.5% fat induces a 5% increase in sleeping metabolic rate compared with the rate prevailing on an isoenergetic diet with less carbohydrate and containing 39% fat. Danforth et al (38) suggest that dietary carbohydrate may have a selective effect on thyroid metabolism, which may explain these subtle differences in energy expenditure.

The metabolic differences between the response to carbohydrate and fat is more readily seen in selective overfeeding studies. On average a 50% increase in energy intakes by overfeeding with carbohydrate leads to a 10% increase in total energy expenditure after 1 wk (32) compared with a 6% increase in a similar regime of fat overfeeding (29). These differences can readily be explained by the greater energy cost of fat deposition when it is synthesized from carbohydrate rather than being simply transferred from dietary fat into the adipose tissue (39). It is not surprising therefore that dietary fat was implicated (40) in explaining an increase in adiposity in populations with a high-fat diet. The susceptibility of individuals to become obese may also be explained by the selective propensity of the pre-obese to store rather than oxidize fat. Changes in substrate intake also cause subtle changes in the respiratory quotient (41, 42) but only minor effects on total energy expenditure. The minor effects on respiratory quotient and energetics are difficult to document but on a cumulative basis could prove to be important in slowly modulating energy balance.

**References**