Importance of Nutrient Balance in Body Weight Regulation

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I. INTRODUCTION

Most individuals maintain a stable body weight over long periods of their lives. This indicates that individual average energy intakes usually vary around the same mean as average energy expenditures. But energy balance is likely to be maintained only if body composition remains constant, since accumulation or depletion of protein, carbohydrate, or fat would in time lead to alterations in food intake. It has long been recognized that the body spontaneously tends to maintain nitrogen balance even though substantial daily deviations occur. Changes in the level of protein intake lead to limited gains or losses in the body's protein mass, but soon the nitrogen balance is achieved again. The mechanisms involved in the maintenance of a constant protein content, although not well understood, operate effectively on diets of very diverse composition, provided that they supply adequate amounts of protein. Since protein balance tends to maintain itself spontaneously, and because protein contributes only a minor fraction of energy intake, it is the metabolism of carbohydrates and of fats that primarily influences the regulation of body weight. The following discussion will consider the manner in which carbohydrate disposal adjusts itself to carbohydrate intake and fat oxidation to fat intake.

II. EFFECTS OF FOOD INTAKE ON METABOLISM

Starch, sugars, and triglycerides provide the bulk of dietary energy, and glucose and fatty acids are the major metabolic fuels used for energy production. In considering the roles of carbohydrates and fats in the regulation of the energy balance, one usually deals with the sum of carbohydrate and fat energy consumed and expended. This is related in part to the belief that excess carbohydrate is readily transformed into fat. Rapid rates of de novo lipogenesis can occur in adult humans, for example during total parenteral nutrition, where large doses of dextrose are often provided to ensure positive energy and nitrogen balances. Fat synthesis can also be induced by sustained, deliberate ingestion of large excesses of carbohydrate. Nonprotein respiratory quotients greater than 1.0, which indicate that the rate of fat synthesis exceeds the concomitant rate of fat oxidation, occur when the body's glycogen stores have reached some 8–10 g per kg body weight. Under normal living conditions, glycogen reserves tend to be spontaneously maintained in the range of 200–400 g. Ingestion of a 500-g load of carbohydrate is accommodated mainly by expansion of the body's glycogen reserves, since the nonprotein RQ will remain below 1.0, except in individuals who have previously consumed a high carbohydrate diet for several days (Figure 1). When normal-sized mixed meals are consumed, the RQ will vary between 0.75 and 0.95. Conversion of carbohydrate to fat does therefore not appear to be an important pathway for the disposal of dietary carbohydrate. Hence, it is possible to consider separately the factors involved in the maintenance of the carbohydrate and the fat balance.

The ingestion of a meal providing nutrients in the same proportion as the fuel mix oxidized in the post absorptive state (i.e., 15% of energy as protein, 35% of carbohydrate, 50% as fat) leads to a prompt increase in the RQ, reflecting an increase in carbohydrate, and a decrease in fat oxidation (Figure 2). This response appears to be determined primarily by the reaction induced by the carbohydrate content of the meal, since essentially the same RQ pattern and changes in circulating...
glucose, insulin, and free fatty acid concentrations are observed after consumption of a meal containing the same dose of protein and of carbohydrate, but only little fat (Figure 2). Thus carbohydrate intake promotes the oxidation of carbohydrate, whereas fat intake does not lead to an increase in fat oxidation.⁶

III. ACHIEVEMENT OF MACRO-NUTRIENT BALANCE

Spontaneous adjustment of the rate of oxidation of a substrate to its rate of intake is obviously a major factor facilitating maintenance of substrate balance. Such adjustments explain why the body spontaneously tends to maintain protein and carbohydrate balances, whereas the achievement of fat balance must depend on mechanisms fundamentally different from those involved in the maintenance of carbohydrate balance.

The essential difference in the manner in which the carbohydrate and fat balances are maintained is particularly well illustrated by data obtained in mice fed ad libitum, for which daily rates of carbohydrate and fat oxidation were assessed by indirect calorimetry during many consecutive days. When diets of fixed composition are consumed, carbohydrate oxidation is proportional to energy (and carbohydrate) intake, whereas fat oxidation is negatively correlated with energy (and fat) intake (Figure 3).⁷ These short-term responses do not account for the fact that stable body weights are commonly achieved on diets with low or high fat contents. Thus, phenomena other than the day-to-day responses illustrated above must be considered to explain how, in the long run, fat oxidation can become commensurate with the average fat intake.

IV. FACTORS CONTROLLING FAT OXIDATION

As can be inferred from the data shown in Figures 1, 2, and 3, the rate of fat oxidation is markedly influenced by the availability of carbohydrate, not only during the postprandial phase when carbohydrate is being absorbed from the gut, but also subsequently when the glycogen reserves are repleted, as shown by the high RQ maintained for many hours after a massive carbohydrate intake. The range within which the body’s glycogen reserves tend to be maintained depends on the diet’s carbohydrate content.⁷ The fact that lower glycogen levels are maintained on diets with a substantial fat content provides a mechanism permitting increased oxidation of fat on such diets.
Fat is made available to tissues for oxidation mainly by release of free fatty acids (FFA) from adipose tissue. The rate of fat oxidation generally varies in parallel with changes in the level of circulating FFA. This correlation is not always very reliable when different situations are compared, which may be due in part to the presence of triglyceride deposits in various tissues, providing fatty acids locally. It is evident, also, that visceral fat stores are turned over more rapidly than peripheral fat deposits, hepatic extraction of FFA from the portal circulation is another factor which may contribute to variability in the relationship between the concentration of FFA in the circulation and the concomitant rates of fat oxidation. Free fatty acid levels tend to increase as the body's adipose tissue mass becomes enlarged. The effect of changes in the adipose tissue mass on FFA levels is limited by the homeostatic regulation of circulating fuel levels. The elevation of circulating insulin levels which is associated with the enlargement of the adipose tissue mass attenuates the impact of changes in the fat mass on circulating FFA levels.

The leverage which FFA exert on the rate of fat utilization can be readily demonstrated by raising their concentration by infusion of triglyceride emulsions. The increase in fat oxidation which ensues has only a minor effect on blood glucose levels in the fasting state, whereas the rate of disposal of a glucose load is markedly reduced when FFA levels are elevated. Artificially raising circulating FFA by triglyceride infusion mimics in effect the changes in glucose tolerance observed in obesity. It can be inferred that expansion of the adipose tissue mass tends to promote fat oxidation, and that this in turn will exert a carbohydrate-sparing effect. Substantial changes in the size of the adipose tissue mass are necessary to provide such leverage, so that this effect is brought into play only through the cumulative effects of prolonged positive, or negative, fat balances. This phenomenon thus affects the use of metabolic fuels in a very different manner from the immediate fat-sparing effect which follows ingestion of carbohydrates.

V. ROLE OF INSULIN RESISTANCE IN THE REGULATION OF BODY WEIGHT

The development of obesity induces insulin resistance. The thermic effect of food tends to be reduced in the face of insulin resistance. The decrease in energy expenditure which this entails has been considered to be a factor promoting further fat accumulation. A reduced sensitivity to insulin, on the other hand, will tend to reduce the rate of glucose oxidation relative to that of fat.
The development of insulin resistance provides a mechanism capable of enhancing the effect which the enlargement of the adipose tissue mass exerts in promoting the oxidation of fat relative to that of glucose. Insulin resistance induced by obesity thus also includes a component which tends to limit the increase in the adipose tissue mass necessary to enhance the fat oxidation to a rate commensurate with dietary fat intake.

VI. DIFFERENCES IN THE STORAGE CAPACITIES FOR GLYCOGEN AND FAT

The differences in the intensity of the metabolic and endocrine responses to changes in the size of the body's glycogen and fat reserves are related to the considerable difference in the body's ability to store glycogen and fat, which entails a factor of about 100-fold. The constant availability of glucose is of paramount importance in assuring an adequate substrate supply for the brain. Since glycogen stores are quite small compared to daily carbohydrate needs, maintenance of carbohydrate balance deserves a far higher priority for the organism than the maintenance of a stable fat content, which is hardly affected by short-term deviations from an even fat balance.

Many of the characteristic differences between the regulation of carbohydrate and fat metabolism can be understood and predicted by considering a simple model comprising two reservoirs of very different dimensions. The small and large reservoirs in Figure 4 are meant to represent the body's limited ability to store glycogen and its large capacity for fat storage. The fuels stored in the two reservoirs both contribute fuel to the turbine, used as an analogy for metabolic energy production. It is assumed in the model that the relative contributions made by the small and large reservoirs to the turbine flux are proportional to the hydrostatic pressures prevailing in the two reservoirs. Replenishment, which occurs from

Figure 3. Daily carbohydrate and fat oxidation in relation to carbohydrate (or fat) and energy intake in 10 female CD1 mice fed ad libitum. They had free access to running wheels and were provided with diets containing 13% (five mice) or 45% (five other mice) of total energy as fat, 18% as protein, and the balance as carbohydrate (half starch, half sucrose). Individual cages were kept in hermetically sealed drums (volume = 220 liters), vented once a day. Food intake, CO2 production, oxygen consumption, and spontaneous running activity were determined daily for 29 consecutive days. Carbohydrate and fat oxidation were calculated by indirect calorimetry, assuming that the mice maintained an even nitrogen balance. (In view of the increase in fat oxidation elicited on the 45% fat diet by extensive running, rates of fat oxidation on this diet were considered only for days on which less than 1,000 revolutions were registered.)
time to time, will considerably alter the level in the small reservoir, while hardly affecting the level in the large reservoir. The contribution from the small reservoir to the turbine flux will therefore increase following each fuel addition, and subsequently decline as its contents are rapidly drained. The behavior in this simple model qualitatively predicts the RQ response to a meal in Figure 2, including the fact that such changes should primarily be dependent on changes in the level in the small reservoir, regardless of the amount added to the fat stores (i.e., the RQ pattern in Figure 2 is the same, regardless of the meal's fat content).

VII. METABOLIC FEEDBACK EFFECTS ON THE CONTROL OF FOOD INTAKE

The fact that the level in the large reservoir hardly changes following replenishment makes it an unlikely site for the detection of variations that could elicit signals capable of triggering replenishment when needed. By contrast, the level in the small reservoir is affected by marked fluctuations during each cycle of depletion and replenishment. These are much more readily detectable, and they can more readily provide a source of signals serving to trigger replenishment at regular time intervals. One is therefore led to expect that the regulation of food intake should be influenced to a much greater extent by changes in the body's glycogen stores than in response to the relatively insignificant changes in its fat reserves. In mice fed ad libitum, gains or losses of glycogen or fat during one day elicit decreases or increases in food intake during the following 24-hour period (Figure 5). However, as shown by comparing the steepness of the slopes in this figure, the strength of the negative feedback effect is much greater for deviations from the carbohydrate balance than for deviations from the fat balance.
VIII. STABILIZATION OF THE BODY FAT MASS

A particularly important behavior revealed by the model is that control of replenishment based on the detection of changes in the level of the small reservoir will allow the achievement of a stable level in the large reservoir, even in the absence of any mechanism capable of detecting such changes. The steady state will simply be achieved when the cumulative effects of imbalances between inflow into and outflow from the large reservoir have led to the situation for which the hydrostatic pressure then prevailing in the large reservoir causes the drain from it during one cycle to be equal to the amount provided to it by one replenishment.

It is of interest to examine the factors which influence the conditions for which this steady state is achieved. When equal amounts of fuel are added to the two reservoirs (middle panels of Figure 5), the steady state will be achieved when the level in the large reservoir is equal to the average hydrostatic pressure in the small reservoir. If the level triggering replenishment in the small reservoir remains constant, then a change in the proportion of fuel added to the two reservoirs will lead to considerable shifts in the content of the large reservoir before steady state conditions are again established, as illustrated by comparing the three upper panels of Figure 4. However, as shown in the lower panels of Figure 4, the level in the large reservoir may remain constant while the proportions of fuel added to it vary, provided that the
levels triggering replenishment be appropriately modified.

In many studies with experimental animals, it has been found that diets with a high fat content lead to marked accumulation of body fat. As illustrated in Figure 6, the leverage exerted by the diet's fat content is gradual, and it is to a large extent reversible. It thus appears that the decrease in the range within which glycogen stores are maintained, as the fat content of the diet increases, is generally not sufficient to permit the rate of fat oxidation to rise to the diet's fat content; and that adjustment of fat oxidation to fat intake is achieved only after a sometimes substantial accretion of the adipose tissue mass. Shifts in the range within which the body's glycogen reserves are maintained, as well as expansion or reduction of the adipose tissue mass, are predictable consequences of variations in the carbohydrate-to-fat ratio of the diet. But whereas the former has only a limited effect on body weight, the latter can become the cause of obesity.

IX. IMPACT OF FOOD AVAILABILITY

The constant availability of palatable foods tends to prevent an appropriate downward adjustment of the range within which glycogen stores are maintained. As suggested by the model shown in Figure 4 (compare in particular the right upper and lower panels), differences in the range within which glycogen reserves are kept will markedly alter the level to which the large reservoir is forced to increase before a steady state is achieved. Furthermore, theoretical studies of this model reveal that this effect is magnified as the diet's fat content becomes increasingly elevated. The considerable variability between animals maintained on high fat diets (cf. the standard deviations in Figure 6) is probably due in part to differences in the glycogen levels which each tends to maintain. This suggests that it may not be necessary to postulate defects in the mechanisms regulating the energy balance to explain the high incidence of obesity in affluent societies, where highly palatable foods with a substantial fat content are constantly available.

X. RQ, FQ, AND STRATEGY FOR WEIGHT CONTROL

In metabolic terms, the steady state of weight maintenance depends on the oxidation of a fuel mix whose average composition matches that of the diet. Regulation of food intake serving to maintain either the carbohydrate, fat, or protein balance is then sufficient, in principle, to adjust total energy intake to overall energy expenditure as well. For reasons cited earlier, adjustment of food intake serving to maintain blood glucose or the carbohydrate balance appears to be the most plausible.

The relative contributions made by glucose and FFA to the fuel mix oxidized are readily determined by measuring the respiratory quotient (RQ). A direct comparison with the carbohydrate-to-fat ratio in the diet is facilitated by defining the food quotient (FQ) as the ratio of CO₂ produced to oxygen consumed during the oxidation of a representative sample of the diet consumed. When the average RQ exceeds the FQ, the fuel mix oxidized contains less fat than the nutrients consumed. Since the regulation of food intake and of carbohydrate oxidation will be such as to prevent depletion of the body's glycogen reserves, a sustained period with an average RQ greater than the FQ implies accumulation of fat. Conversely, when the average RQ is less than the diet's FQ, the fuel mix oxidized...
contains more fat than supplied by the diet. Since food intake is limited to providing a carbohydrate intake commensurate with carbohydrate oxidation, net withdrawal of fat from the adipose tissue stores then occurs.

As shown in Figure 7 (upper panel), the RQ increases with the amount of food consumed. The parameters defining these correlations are related to the diet’s fat content. The relationships can be normalized by considering variations of the RQ/FQ ratio as a function of the ratio of energy intake to energy expenditure (lower panel of Figure 7). Excepting the unusual situation where limited amounts of fat only are consumed, it can be said that maintenance of an RQ lower than the FQ is a necessary and sufficient condition for weight loss. This formulation offers more guidance than the statement that the energy intake must be less than the energy expenditure to achieve weight loss (which is another, and usually considered the “necessary and sufficient” condition). Instead of having simply to rely on counting calories in order to ensure that less energy is eaten than is being burned, the RQ/FQ concept helps one to realize that it must be easier to maintain the average RQ below the diet’s FQ when consuming a diet with a high FQ (i.e., a diet high in carbohydrates, and low in fats).

XI. IMPACT OF EXERCISE ON RQ AND ENERGY BALANCE

Consideration of the RQ relative to the FQ also provides a basis for appreciating the leverage...
of physical activity in the regulation of body weight. Sustained (aerobic) exercise leads to a gradual decline in the RQ.\textsuperscript{27} This provides another leverage in helping to bring the average RQ below the level of the FQ. This point is illustrated by the data shown in Figure 8, obtained in mice fed ad libitum and having free access to a running wheel. Increases in spontaneous exertion, measured by the number of revolutions of the running wheel per day, led to a decrease in the RQ. The increment in the amount of food consumed to maintain carbohydrate balance then fell short of matching the increase in energy expenditure, leading to a negative energy balance (lower panel in Figure 8).

XII. REGULATION OF FOOD INTAKE VERSUS REGULATION OF ENERGY EXPENDITURE

The experiments described above also reveal that the energy balance in these mice fed ad libitum is much more powerfully influenced by changes in the amounts of food consumed ($R^2 = 0.43$ and 0.41) than by variations in energy expenditure ($R^2 = 0.03$ and 0.10) (Figure 9). This indicates that adjustment of energy intake to energy expenditure, rather than the reverse, appears to be primarily responsible for the maintenance of energy balance and body weight.

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Figure 8. Effect of spontaneous running activity on 24-hour RQs and daily energy balances in mice fed ad libitum and maintained on diets containing 13% or 45% of energy as fat, 18% as protein, and the remainder as carbohydrate. The data were obtained in two groups of five mice over a period of 29 days (see legend to Figure 3 for further details).
Obese subjects maintain the energy balance over prolonged periods of time, often in spite of dietary and lifestyle habits whose combined impact would be predicted to induce rapid weight gain. This suggests that the regulation of food intake in obesity is not necessarily deficient, but rather that the steady state of weight maintenance, where the average RQ is equal to the FQ, is reached for these individuals only after a substantial expansion of the adipose tissue mass has occurred. Various combinations of genetic, dietary, as well as lifestyle factors contribute to bringing about individual differences in this regard.

XIII. CONCLUSIONS

The range within which glycogen levels are maintained and the size of the adipose tissue mass appear to play important roles in complementing the body's metabolic and endocrine regulatory responses. Together these lead to the oxidation of a fuel mix whose composition matches the nutrient distribution in the diet. The carbohydrate-to-fat ratio in the diet is thus a significant factor in determining for which body composition the steady state of weight maintenance will be maintained. Increases in the size of the adipose tissue mass should be expected when the fat content of
the diet is raised. This is particularly the case when the constant availability of highly palatable foods makes a spontaneous reduction of the range within which glycogen levels are maintained less likely, and when sustained physical activity capable of enhancing fat oxidation is not part of the daily routine.

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References