A peripheral perspective of weight regain

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BODY WEIGHT REGULATION is sensitive to a number of environmental, social, and genetic pressures but is ultimately subject to a homeostatic control system linked with adiposity (23, 36). This control system involves a closed-feedback loop between the central nervous system and the peripheral tissues, whereby the central nervous system interprets a complex set of signals from the periphery and subsequently sends signals to defend a certain level of body weight and fat mass. As such, there are metabolic adjustments with overfeeding and weight gain that promote weight loss (22). However, the global obesity epidemic provides evidence that the other pressures affecting body weight cannot only override these protective metabolic adjustments but can also alter the control system in a somewhat permanent fashion by gradually elevating the defended level of adiposity. In addition, there are metabolic adjustments with caloric restriction and weight loss that work to regain the lost weight (22, 24, 26, 27). Although the other pressures affecting body weight can be used to override these metabolic adjustments, there is little evidence of an equivalent readjustment of the control system to lower its targeted adiposity level. It is this persistence of the control system and its metabolic adjustments in the face of downward fluctuations in adiposity that explain the most critical problem in obesity treatment: keeping the weight off after weight loss. It is for this reason that significant efforts have been made to increase our understanding of the metabolic drive to regain weight.

One of the most fundamental metabolic adjustments in response to weight reduction is the large positive energy imbalance, or “energy gap,” between intake and expenditure (26). In both humans and rodents, the drive to consume food increases and energy expenditure decreases. In order to maintain the reduced weight, the food provision must be reduced to match the suppressed level of expenditure. When this limitation on food provision is not maintained, food is ingested in gross excess of expenditure, the extra energy is stored, and weight is gained. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Evans et al. (9) report an interesting set of observations that describe this metabolic drive in two strains of rats in response to two weeks of caloric restriction. These authors have used an impressive array of metabolic monitoring tools to follow these animals prospectively through caloric restriction and the early part of the relapse to the defended body weight. Long-Evans rats responded with hyperphagia that was persistently higher than ad libitum-fed controls through 8 days of refeeding, while expenditure appeared to resolve within a few days. In contrast, the Sprague-Dawley rats had an expenditure that was still suppressed after 8 days of refeeding, while intake was higher for only the first day. The authors use this divergent response to suggest that the homeostatic response to caloric restriction may selectively target appetite or expenditure to restore body weight.

As Evans et al. (9) have pointed out in their discussion, there are neural pathways that have a more profound influence on one side of the energy balance equation, and there may be others yet unidentified that are even more specific for intake or expenditure. Complicating the distinction is the thermic effect of food, which effectively increases expenditure as more food is consumed. In any case, the practical lesson from this interesting study is that differential genetic pressures may yield divergent responses to energy restriction in order to achieve the same energy gap and rate of weight regain. This is a critical consideration when pursuing therapeutic strategies that target the metabolic drive to regain for the purposes of facilitating sustained weight reduction. The implication is that therapies targeting a single factor or component of the metabolic drive to regain weight may not be effective for everyone. It is not surprising that exercise, with broad and numerous effects on metabolism, appears to be the most potent approach to facilitating sustained weight reduction (3, 18, 19, 23).

While much attention has been given to the neural pathways that are involved in the regulation of energy balance, less has been given to other metabolic adjustments in the periphery that contribute to the drive to regain. Indirect evidence of one such adjustment comes from the respiratory quotient (RQ) observed by Evans et al. (9) and others (6, 12, 27). During regain when there is a chronic positive energy balance, there is also a dramatic shift in fuel utilization that promotes an energetically efficient deposition of fat stores (8). Glucose becomes the preferred fuel for energy needs, and fatty acid oxidation is suppressed. The consequence is the diversion of ingested fats to the adipose stores (4). This shift is important in that the ingested lipid is stored with little energetic expense, while glucose must go through the energetic costly process of lipogenesis (10). Therefore, for the same amount of consumed energy, more weight will be gained if the ingested fat is stored and the carbohydrate is used for energy. One additional consideration in this discussion, however, is that de novo lipogenesis is likely occurring during weight regain, an effect that will elevate RQ and make it less reflective of substrate oxidation (13). As Evans et al. (9) point out in their study, the RQ above 1.0 in refeeding rats is a fairly good indication that a significant amount of lipogenesis is occurring (1). Without fuel tracers, it is difficult to distinguish between the respective contribution of the shift in fuel oxidation and of lipogenesis to the elevation in RQ. However, under these conditions of a large positive energy
Undoubtedly, the substantial progress in recent years that has led to the high rates of relapse to the obese state in humans. The underlying mechanisms that are responsible for these dramatic changes in fuel metabolism can be linked to the large energy imbalance and the accompanying excursions in circulating levels of glucose and insulin throughout the day. First, insulin has potent suppressive effects on the release of endogenously stored lipid (16). Depending on the size of the lipid component in the diet, this antilipolytic effect would likely lead to reduced fatty acid availability in hepatic and skeletal muscle. Second, insulin and glucose lead to the production of malonyl-CoA (6, 32, 35). Malonyl-CoA is not only a potent inhibitor of carnitine palmitoyl transferase I (2, 28), but it also is the required substrate for fatty acid synthetase. As such, the elevation of malonyl-CoA suppresses fatty acid oxidation while directing excess substrate to de novo lipogenesis. When energy restriction is followed by ad libitum feeding, studies have consistently shown an elevation in malonyl-CoA and a suppression in fat oxidation (30–32).

In addition to these immediate effects on lipolysis and tissue metabolism, insulin and glucose induce the expression of a host of genes in the liver, muscle, and adipose tissue that have a more sustained effect on fuel metabolism. There is substantial evidence that these effects are mediated, at least in part, by sterol response element binding protein 1c (SREBP-1c) (11, 15, 20, 21, 34). A number of models that have employed a period of energy restriction followed by refeeding have shown that SREBP-1c and its target genes are dramatically induced in liver, adipose, and skeletal muscle tissues (5, 7, 14, 17, 29, 33). The direct and indirect targets of SREBP-1c are enzymes that promote oxidation of carbohydrates and the synthesis and accumulation of fatty acids and triglycerides. SREBP-1c has been implicated in increasing the expression of acetyl-CoA carboxylase, fatty acid synthase, ATP-citrate lyase, and a number of genes in the glycolytic pathway. The consequences of increased SREBP-1c expression are an enzymatic profile with enhanced glycolytic and lipogenic capacities, essentially magnifying the immediate effects of insulin and glucose on fuel metabolism in these tissues.

There are two reasons why these peripheral aspects of fuel metabolism may be important to consider in the process of weight regain. First, because it is energetically efficient, the trafficking of ingested fats into the adipose depots contributes to a higher rate of regain and a quicker return to the defended level of adiposity. Second, an increased capacity to clear excess fuels into the lipid depots may act through nutrient sensing systems (25) to extend or increase bouts of feeding, a continuing positive energy balance, and further weight gain. Within this scheme, the rate of regain declines as the capacity of adipose tissue limits the ability of these peripheral metabolic adjustments to traffic ingested fats to adipose tissues and rapidly clear excess fuels. Although these metabolic adjustments in the periphery would not be expected to explain all aspects of weight regain, they may be playing a significant role in the high rates of relapse to the obese state in humans. Undoubtedly, the substantial progress in recent years that has furthered our understanding of the neural pathways that are involved in body weight regulation (23, 36) will be critical in designing effective strategies that counter the metabolic drive to regain weight after weight loss. It is critical to remember, however, that the signals controlling those pathways are likely to come from the periphery, where the weight actually lies. From a peripheral perspective, it is this researcher’s opinion that we need to further our understanding of fuel utilization and accumulation during the process of regaining lost weight, and how the flux through these pathways link to the neural pathways controlling energy balance.

REFERENCES

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GRANTS

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