HYPOTHESIS

Carbohydrates, insulin, and obesity

Insulin plays a role in body fat regulation independent of dietary carbohydrates

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The primary cause of common human obesity remains uncertain. There are several plausible explanations, including the popular "carbohydrate-insulin" model (CIM), which suggests that body-fat gain results from consumption of carbohydrates that stimulate postprandial insulin, which promotes energy storage and further intake in a vicious cycle. The theoretical basis of the CIM has been refuted by several recent experiments. We suggest that although insulin plays an important role in body fat regulation, the CIM fails because it focuses on the direct action of insulin on adipose tissue after the consumption of a meal containing carbohydrates. Rather, we propose that the role of insulin in obesity may be better understood by considering its pleiotropic action on multiple organs that is driven by factors mostly independent of carbohydrate intake. Reconsidering the role of insulin may improve our understanding of the causes of obesity and its treatment.

The CIM puts the adipocyte at center stage by highlighting the role of insulin in promoting fat storage and inhibiting its release (*1*). Carbohydrate consumption stimulates insulin secretion, which partitions circulating fuels (such as triglycerides) toward storage in adipose tissue. This is postulated to reduce the energy available for metabolically active tissues such as skeletal muscle. Deprived of fuel, these nonadipose tissues experience a state of cellular "internal starvation" that motivates the individual to respond as they would to actual starvation—by seeking and consuming more food and reducing metabolic rate to conserve energy. Therefore, according to the CIM, excess energy consumption is the result of adipose tissue fat storage due to carbohydrate-driven postprandial insulin. The corresponding "obesity solution" is to replace carbohydrates with dietary fat, which does not stimulate postprandial insulin secretion: the so-called low-carb, high-fat or "ketogenic" diet.

Conceptually, testing the CIM should be simple: Randomize people to consume different diets varying widely in carbohydrates and fat and then measure obesity prevalence in each diet group. But such an experiment, if prolonged, raises ethical concerns due to potential harm to health, and if short, raises questions about whether the absence of effects was due to the short duration. Moreover, ensuring adherence to the assigned diets is not currently possible in people living outside a laboratory setting. A good (but imperfect) solution is to perform the studies on experimental animals, with the caveat that improved experimental control comes at the expense of failing to completely capture the complexity of the situation in humans.

In this context, a large dietary manipulation study exposed mice to 29 different diets to address the impact of diet composition on body fatness (*2*). In 16 of these diets, the macronutrient manipulations allowed a direct test of the predictions of the CIM because protein was held constant (in 8 diets at 10% and 8 diets at 25%) while fat and carbohydrate varied reciprocally between 10 and 80%. The carbohydrates were a mix of corn starch, maltodextrin, and sucrose (typically regarded as refined "high glycemic index" carbohydrates that induce high blood glucose and insulin responses). The mice were exposed to the diets for 12 weeks, which is roughly equivalent to 9 years in humans. The CIM prediction is that as dietary carbohydrate increased, so would postprandial insulin, and the mice would develop obesity and eat more total calories. However, the opposite happened. Mice feeding on diets with a high proportion of carbohydrates ate fewer calories and gained both less body weight and body fat despite higher postprandial insulin. Although this appears to refute the CIM, uncritical extrapolation from mice to humans is problematic.

Although controlled feeding studies lasting multiple years in humans are not feasible, the CIM can be tested by examining its predictions using shorter-term experiments. For example, if individuals are exposed to diets with very different proportions of fat and carbohydrate, the CIM predicts that a high-carbohydrate diet will result in greater postprandial blood insulin concentrations that drive fat accumulation in adipose tissue, thereby increasing hunger and energy intake compared to a low-carbohydrate diet. This prediction was tested in a month-long inpatient metabolic ward study where 20 adults were randomized to receive a diet composed of ~10% carbohydrate, ~75% fat or a diet with ~10% fat, 75% carbohydrate and instructed to eat as much or as little as they wanted (*3*). After 2 weeks, participants switched to the alternate diet. In accordance with CIM predictions, the high-carbohydrate diet resulted in much higher concentrations of circulating postprandial insulin and therefore should have partitioned more energy to body fat storage, thereby increasing hunger and energy intake compared to the low-carbohydrate diet. However, ~700 kcal/day less food was consumed on the high-carbohydrate diet, and participants reported both diets to be equally satisfying and pleasant with no differences in hunger or fullness. Furthermore, despite substantially higher daily insulin secretion, only the high-carbohydrate diet resulted in significant body fat loss.

Although this was a relatively short-term experiment, another study found significantly increased satiety after 10 to 15 weeks of consuming a high-carbohydrate diet compared with a low carbohydrate diet (*4*). Furthermore, a 1-year study in freely living individuals randomized to consume low-carbohydrate versus high-carbohydrate diets found no sustained differences in objective measurements of energy intake (*5*). As a result, long-term average weight loss was almost identical, and individual differences in postprandial insulin secretion did not predict who lost most weight on each diet (*6*). Therefore, the energy intake predictions of the CIM failed to materialize in both short-term and long-term studies.

The CIM also predicts that decreased insulin secretion during a low-carbohydrate diet should increase body fat loss by mobilizing fat trapped in adipose tissue, thereby restoring the fuel supply to metabolically active tissues, compared with an isocaloric diet with higher carbohydrate. Alleviation of cellular "internal starvation" in these tissues should therefore increase energy expenditure. Two studies admitted participants with overweight or obesity to metabolic wards with strict control over food

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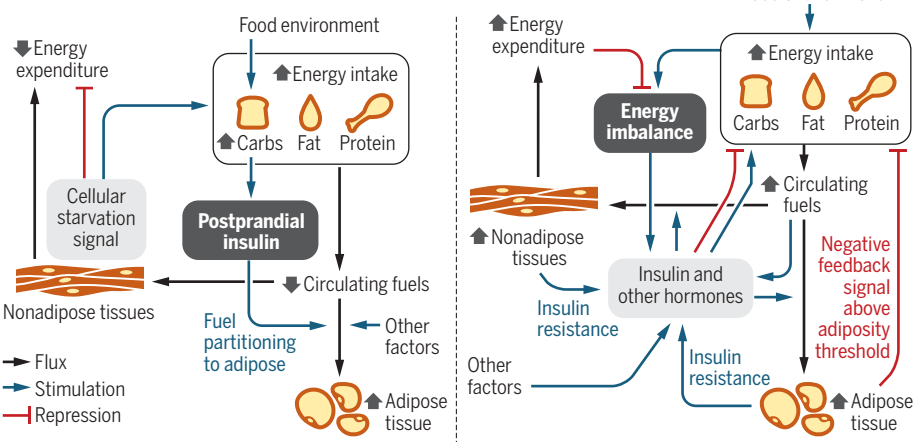
intake for 1 to 2 months and showed that although carbohydrate restriction led to substantial decreases in daily postprandial insulin secretion, both studies found less body fat loss with carbohydrate restriction compared with isocaloric high-carbohydrate diets (*7*, *8*). In one study, the reduced carbohydrate diet led to a significant decrease in energy expenditure (*7*). In the other study, a low-carbohydrate ketogenic diet led to a small, transient increase in energy expenditure that dissipated within a few weeks (*8*).

Two models of body weight regulation



Carbohydrate insulin model
A food environment promoting increased carbohydrate intake stimulates postprandial insulin, which partitions circulating ingested fuels into adipose tissue. This reduces the flux of these fuels into nonadipose tissues, leading to a cellular starvation signal with two consequences: reduced energy expenditure and further stimulation of intake.

Energy balance model
Energy imbalance is driven by increased energy intake caused by the obesogenic food environment. Insulin facilitates the uptake of circulating fuels and provides a negative feedback signal to the brain, which regulates intake in combination with other hormones and signals from adipose tissue when adiposity rises above a critical level.

In contrast to these inpatient controlled feeding studies, two outpatient studies reported increased energy expenditure during low-carbohydrate diets in people who were weight-stable following a period of weight loss (*9*, *10*). However, these results were likely due to a miscalculation of energy expenditure (*11*). Indeed, the reported energy expenditure increases in people on low-carbohydrate diets were not consistent with differences in body weight or measured components of energy expenditure such as resting metabolic rate, physical activity, or skeletal muscle work efficiency. Supporting the absence of effects on energy expenditure, in the mouse study of 29 diets (*2*) there were no effects of variable carbohydrate content on energy expenditure or physical activity.

Supporters of the CIM have criticized the human and mouse experiments that failed to confirm CIM predictions. The test diets in the mouse study were claimed to be inadequate. The human experiments were argued to be too short. We propose that these data should not be ignored, but rather should inform an improved model in agreement with the data (see the figure). Although the "carbohydrate" half of the CIM is disputed by recent experimental tests, this does not discount an important role for insulin in regulating body fat. Genetic manipulation of insulin secretion in mice (*12*) or pharmacologic inhibition of insulin secretion in humans (*13*) can lead to reduced body fat in the absence of diabetes. People with diabetes often experience weight loss prior to diagnosis, and treatment that increases endogenous insulin secretion or exogenous insulin therapy often results in weight regain. Nevertheless, hyperinsulinemia is not associated with meaningful differences in adiposity, and hyperinsulinemia does not necessarily result in increased weight or reliably predict future weight changes (*14*). Furthermore, genetic polymorphisms derived from genome-wide association studies for body mass do not identify targets linked to insulin action in adipose tissue as important causal variants for obesity. Therefore, the extent to which susceptibility to obesity is explained by differences in insulin secretion or insulin action is uncertain, but direct action of carbohydrate-driven postprandial insulin on adipose tissue is unlikely to be the dominant driver of common obesity, as proposed by the CIM.

Postprandial insulin is not the most important factor regulating adipose uptake and storage of fat, which can occur without increasing circulating insulin above basal concentrations (*15*). Basal insulin may be more important because adipose tissue release of fat is exquisitely sensitive to changes in insulin around basal levels, but the effect of insulin quickly saturates in the postprandial range and therefore may be relatively insensitive to dietary carbohydrate. Furthermore, reduction of dietary fat decreases basal insulin to a similar degree as isocaloric reduction in carbohydrate (*7*), indicating that basal insulin concentrations respond to the imbalance between energy intake and expenditure as much as diet composition per se.

Insulin has pleiotropic effects on multiple organs, and its role in body fat regulation is best understood as part of a dynamic network of factors controlling and mediating the effects of energy imbalance. For example, insulin provides a negative feedback signal to the brain that combines with signals from adipose tissue when body fat rises above a critical threshold concentration and serves to regulate energy intake. Adipose tissue and ectopic fat deposition in nonadipose tissues can also drive insulin resistance, thereby affecting circulating insulin concentrations independent of dietary carbohydrate. Therefore, the mechanisms underlying the effects of insulin on adiposity are more complex than proposed by the CIM. Failure of the CIM should not be taken to mean that low-carbohydrate, high-fat diets cannot be beneficial for weight loss. However, direct modulation of the carbohydrate-insulin axis in adipose tissue is unlikely to be the primary mechanism underpinning body fat loss in individuals successfully engaged in such diets. A new model of the role of insulin in obesity is required that is commensurate with data refuting key aspects of the CIM. ■

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