European Journal of Clinical Nutrition (2017), 1–4

www.nature.com/ejcn

REVIEW

A review of the carbohydrate–insulin model of obesity

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The carbohydrate–insulin model of obesity theorizes that diets high in carbohydrate are particularly fattening due to their propensity to elevate insulin secretion. Insulin directs the partitioning of energy toward storage as fat in adipose tissue and away from oxidation by metabolically active tissues and purportedly results in a perceived state of cellular internal starvation. In response, hunger and appetite increases and metabolism is suppressed, thereby promoting the positive energy balance associated with the development of obesity. Several logical consequences of this carbohydrate–insulin model of obesity were recently investigated in a pair of carefully controlled inpatient feeding studies whose results failed to support key model predictions. Therefore, important aspects of carbohydrate–insulin model have been experimentally falsified suggesting that the model is too simplistic. This review describes the current state of the carbohydrate–insulin model and the implications of its recent experimental tests.

European Journal of Clinical Nutrition advance online publication, 11 January 2017; doi:10.1038/ejcn.2016.260

INTRODUCTION

Obesity is defined as an excess accumulation of body fat, and understanding obesity at the most basic level requires knowledge of how adipose tissue fat storage and mobilization are regulated. Insulin has a major role in modulating the activity of several enzymes whose net effect is to promote the uptake, retention and net storage of fat in adipose tissue.[1] These basic facts of adipose tissue physiology, along with the observation that dietary carbohydrates are the primary driver of insulin secretion, have led to the hypothesis that high carbohydrate diets are particularly fattening.

In particular, the 'carbohydrate–insulin model' of obesity posits that diets with a high proportion of carbohydrate elevate insulin secretion and thereby suppress the release of fatty acids from adipose tissue into the circulation and direct circulating fat toward adipose storage and away from oxidation by metabolically active tissues such as heart, muscle and liver.[2–5] This altered fuel availability is theorized to lead to a state of cellular 'internal starvation' leading to adaptive decreases in energy expenditure and increased hunger.[2,5–7] Therefore, the positive energy balance associated with development of obesity is purported to be a consequence of the insulin-driven shift in fat partitioning toward storage in adipocytes, which decreases energy expenditure and increases food intake in an attempt to remediate the cellular internal starvation of metabolically active tissues. Rather than being a passive accumulator of fat as a result of overeating, the carbohydrate–insulin model suggests that endocrine dysregulation of adipose tissue is the primary driver of positive energy balance.

The carbohydrate–insulin model provides a plausible explanation of why insulin therapy tends to cause weight gain in people with diabetes[8] and why outpatient diet trials comparing low carbohydrate diets to others tend to show greater short-term weight loss despite low carbohydrate diets being unrestricted in calories.[9–11] Several popular books have promoted the carbohydrate–insulin model to the public as the reason why they have gained excess weight in the past and why they should follow a low carbohydrate, high fat diet for weight loss.[12–14] However, despite the apparent explanatory power of the carbohydrate–insulin model, its scientific basis is questionable and recent studies have challenged key predictions of the model.

SCIENTIFIC MODELS AND THE PRINCIPLE OF EXPERIMENTAL FALSIFICATION

Scientific models seek to integrate a variety of data and explain a set of observations about a system within an overarching theoretical and mechanistic framework. Experimental confirmation of a model's predictions provides support for the validity of the model and repeated confirmations may eventually lead to widespread acceptance of the model as the scientific standard. However, scientific models cannot be proven to be true. Rather, models represent provisional representations of our understanding, and countering evidence may require substantial model corrections or possibly outright rejection of the model. Importantly, scientific models go beyond providing putative explanations and make experimentally testable predictions that are capable of falsifying the models.[15]

As model falsification is relatively rare in the field of nutrition, I will use a well-known example from physics to illustrate the process.[16] In the late nineteenth century, physicists postulated that light propagated as a wave through a medium called the 'luminiferous ether'. Like the carbohydrate–insulin model, the ether model seemed highly plausible as the wave-like nature of light was well-known and all other waves propagated through a medium. It was difficult to conceive how a wave could propagate through a vacuum without a medium and scientists readily accumulated evidence in favor of the ether model. (For example, comet tails were thought to be caused by 'ether drag' as they moved through the medium.) The ether model explained a lot and it made sense. Unfortunately, it was also wrong.

As with all scientific models that attempt to explain certain phenomena, the ether model made predictions that were

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Received 15 September 2016; accepted 10 October 2016

experimentally testable. More specifically, experiments can be designed that are capable of falsifying the model meaning that failure of any necessary model prediction requires that the model be abandoned as either too simple or simply incorrect. It does not matter how many model predictions are successfully confirmed by the experiment, failure of any single prediction means that the model is falsified.

For the ether model of light propagation, falsification came with the classic Michelson–Morley experiment in 1887 that failed to detect a significant difference in the speed of light moving in different directions through the hypothesized ether. Since then, several more definitive experiments were conducted that confirmed these results. The experimental falsifications of the ether model did not imply that light does not have wave-like properties, but the simple ether model of light propagation was untenable.

EXPERIMENTAL FALSIFICATION OF THE CARBOHYDRATE–INSULIN MODEL

Whereas some models of obesity are so complex that it is difficult to know where to begin when assessing their validity,[17] the carbohydrate–insulin model provides clear experimentally testable predictions. For example, the carbohydrate–insulin model predicts that diets with decreased proportion of carbohydrate to fat, but identical protein and calories, will reduce insulin secretion, increase fat mobilization from adipose tissue and elevate fat oxidation. The altered metabolic and hormonal milieu associated with reduced dietary carbohydrate will therefore relieve the state of cellular internal starvation resulting in decreased hunger, increased body fat loss and increased energy expenditure compared with an isocaloric diet with higher carbohydrates and higher insulin secretion.[2] If any of these predictions fail, then the carbohydrate–insulin model is falsified and a more commensurate model must be sought.

Testing the model predictions requires inpatient feeding studies as diet adherence cannot be guaranteed in outpatient studies.[18] Recently, two metabolic ward studies directly tested the logical consequences of the carbohydrate–insulin model in humans.[19,20] Both studies were conducted while subjects were continuously residing in metabolic wards where they consumed carefully controlled diets. Both studies found the expected rapid and sustained decrease in insulin secretion when dietary carbohydrates were restricted. Therefore, the experimental conditions required to test the predictions of the carbohydrate–insulin model were fully satisfied.

In concordance with the model predictions, carbohydrate restriction led to increased fat oxidation reaching a maximum within a few days and remaining constant thereafter. However, neither study found the predicted augmentation of body fat loss with carbohydrate restriction. Rather, despite the reduction in insulin secretion, both studies found slightly less body fat loss during the carbohydrate restricted diets compared with isocaloric higher carbohydrate diets with identical protein.[13,14] 19, 20

In one study, the reduced carbohydrate diet led to a significant decrease in energy expenditure, both during sleep and throughout the day, a result counter to the carbohydrate-insulin model.[19] In the other study, a very low carbohydrate ketogenic diet led to increased daily energy expenditure of only 57 kcal/day, and the effect waned over time.[20] Although this small energy expenditure increase during the ketogenic diet was in the direction predicted by the carbohydrate–insulin model, it was quantitatively much less than what was expected. Specifically, the effect size of the pre-specified primary energy expenditure outcome was substantially smaller than the 150 kcal/day threshold determined in advance to be the smallest change that would be considered physiologically important. Furthermore, the observed energy expenditure effect was several-fold lower than the 400–600 kcal/day effect previously estimated to be the 'sizable metabolic advantage' of a very low carbohydrate diet[21] and incompatible with the popular claim of Dr Robert Atkins that such diets increase energy expenditure to an extent that they offer a 'high calorie way to stay thin forever'.[12]

CONCORDANCE WITH PREVIOUS INPATIENT FEEDING STUDIES

Despite achieving the desired differences in insulin secretion via isocaloric manipulation of dietary carbohydrate and fat, the recent studies[19,20] clearly demonstrated that the energy expenditure and body fat predictions of the carbohydrate–insulin model failed experimental interrogation. These results are in accord with previous inpatient controlled feeding studies that have either found small decreases in energy expenditure with lower carbohydrate diets[22–25] or reported no statistically significant differences[26–35] when comparing diets with equal calories and protein, but varying carbohydrates from 20 to 75% of total calories. Furthermore, the small effects on body fat loss were similar to those of previous inpatient feeding studies finding no significant differences in body fat resulting from isocaloric variations in carbohydrate and fat.[30,36–39]

There has never been an inpatient controlled feeding study testing the effects of isocaloric diets with equal protein that has reported significantly increased energy expenditure or greater loss of body fat with lower carbohydrate diets. However, a recent outpatient study reported that during a weight loss maintenance period, the total energy expenditure was significantly increased by 325 kcal/day during a 28-day very low carbohydrate diet compared with an isocaloric low fat diet with 50% less protein.[40] Although these results have been offered in support of the carbohydrate–insulin model,[2] such an interpretation is confounded by the differences in dietary protein which is known to be thermogenic.[41,42] Furthermore, there are serious concerns about diet adherence and the accuracy of the energy expenditure measurements as these data were inconsistent with the lack of significant changes in body weight or composition over the 3-month test period despite total energy expenditure being ~ 200–500 kcal/day greater than the reported energy intake.[43]

Another recent outpatient controlled feeding study examined the effect of dietary carbohydrate and glycemic index on body weight and composition during periods of sequential overfeeding, underfeeding and refeeding with isocaloric diets containing equal protein.[44] Although there were no statistically significant differences in body fat changes between the diet groups, the highest carbohydrate and glycemic index diet exhibited a trend toward greater body fat regain during refeeding that amounted to an increased rate of energy storage of ~ 400–500 kcal/day.

This pair of marginally supportive outpatient controlled feeding studies[40,44] suggests that perhaps the weight-reduced state is required to unveil the effects of lower carbohydrate or reduced glycemic index diets to improve energy expenditure and body fat. This possibility deserves further investigation.

AD HOC MODIFICATIONS OF THE CARBOHYDRATE–INSULIN MODEL

Although it is always possible to propose various ad hoc modifications of a model to subvert apparent experimental falsification, at some point a decision needs to be made to reject the model and formulate an alternative that is more commensurate with the data. Ad hoc complexifications of the luminiferous ether model were proposed, going so far as suggesting that the length of measurement devices shrank in the direction of motion through the ether—the so-called Lorenz–Fitzgerald length contraction.[16] Shrinking the experimental apparatus by just the right tiny amount could save the ether model, but this proposal seemed highly contrived. In 1905,

Einstein explained the Lorentz–Fitzgerald contraction as being a natural consequence of his special theory of relativity that did not require a medium for light propagation. The ether model was finally dead and buried.

Ad hoc modifications of the carbohydrate–insulin model include the possibility that the downstream effects of reduced insulin secretion take more time to come to fruition, and the experiments were not long enough to observe these effects. For example, perhaps fat oxidation further increases over more prolonged periods of carbohydrate restriction, thereby leading to an acceleration of body fat loss. However, daily fat oxidation was observed to plateau within the first week of the reduced carbohydrate diets as indicated by the rapid and sustained drop in daily respiratory quotient.[19,20] As further evidence that adaptations to carbohydrate restriction occur relatively quickly, adipose lipolysis is known to reach a maximum within the first week of a prolonged fast[45] as does hepatic ketone production.[46] Although there is some evidence that exercise performance may increase over several weeks of adaptation to a low carbohydrate diet,[47] there is no evidence for acceleration of daily fat oxidation.

Another ad hoc modification of the carbohydrate–insulin model of obesity suggests that it only applies to certain people, perhaps those who are sufficiently intolerant to dietary carbohydrates. In that case, our recent experiments[19,20] and all previous inpatient studies[22–28,30–39] failed to confirm the model predictions because they were performed in the wrong subjects. Although this possibility cannot be excluded, it severely limits the generalizability of the carbohydrate–insulin model to an extent that it is highly unlikely to explain the general features of common obesity and its increasing prevalence.

Perhaps the predicted increase in energy expenditure with carbohydrate restriction occurs not through changes in metabolic rate, but rather via increased spontaneous physical activity. Therefore, such effects may not have been observed while subjects resided as inpatients on metabolic wards that limited their physical activities. Some support for this possibility was provided in the recent study that found a statistically nonsignificant 126 kcal/day increase in spontaneous physical activity energy expenditure on the days spent outside the metabolic chamber at the end of the 2-month inpatient stay when the subjects were consuming the ketogenic diet.[20] However, this trend for increased physical activity expenditure could also be interpreted as the result of the subjects' behavior being affected by the time spent on the metabolic wards rather than an effect of the ketogenic diet. Nevertheless, a modest effect of carbohydrate restriction on spontaneous physical activity is certainly plausible and might be amplified under free-living conditions.

Finally, it may be that the carbohydrate–insulin model operates primarily by affecting energy intake such that low carbohydrate diets decrease hunger, reduce appetite and promote satiety without offering any particular metabolic advantage for body fat loss. This aspect of the carbohydrate–insulin model was not directly examined in the recent studies as food intake was strictly controlled.[19,20] Under ad libitum feeding conditions, the possible effect of decreased carbohydrates and insulin per se may be difficult to dissociate from the effects of increased dietary protein that often accompanies carbohydrate restriction which may independently promote satiety, decrease overall energy intake, as well as increase energy expenditure, and beneficially influence energy partitioning and body composition.[41,42] Nevertheless, very low carbohydrate diets with limited protein likely reduce appetite by promoting an increase in circulating ketones,[48] although the mechanism for this effect is unclear.[49]

IMPLICATIONS AND CONCLUSIONS

It is important to emphasize that low carbohydrate diets may offer metabolic benefits beyond loss of weight and body fat[50] regardless of whether the carbohydrate–insulin model is true or false. Furthermore, experimental falsification of important aspects of the carbohydrate–insulin model does not mean that dietary carbohydrates and insulin are unimportant for body fat regulation. Rather, their role is more complicated than the carbohydrate–insulin model suggests as differences in energy expenditure and body fat have been observed to occur in diametrically opposite directions than were predicted on the basis of differences in carbohydrate intake and insulin secretion.[19,20]

The rise in obesity prevalence may be primarily due to increased consumption of refined carbohydrates, but the mechanisms are likely to be quite different from those proposed by the carbohydrate–insulin model. For example, such diets may lead to greater overall energy intake by increasing palatability, increasing appetite or decreasing satiety.

Reasonable ad hoc modifications of the carbohydrate–insulin model have been proposed, but the revised model relies on hypothesized effects of carbohydrates and insulin to alter energy intake and spontaneous physical activity, both of which remain to be demonstrated experimentally.

An intriguing possibility is that several predictions of the carbohydrate–insulin model may come to fruition during maintenance of lost weight or weight regain as suggested by recent outpatient studies.[40,44] If so, this implies that reduced carbohydrate diets may be beneficial for prevention of weight regain following weight loss.

CONFLICT OF INTEREST

I have received funding from the Nutrition Science Initiative to investigate the effects of ketogenic diets on human energy expenditure. I also have a patent pending on a method of personalized dynamic feedback control of body weight (US Patent Application No 13/754 058; assigned to the National Institutes of Health).

ACKNOWLEDGEMENTS

This research was supported by the Intramural Research Program of the NIH, National Institute of Diabetes and Digestive and Kidney Diseases.

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