

The Energy Balance Model of Obesity: Beyond Calories In, Calories Out

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Abbreviations: AgRP: agouti-related peptide; ATGL: adipose triglyceride lipase ; BMI: body mass index; CGI58: comparative gene identification-58; CIM: carbohydrate-insulin model; EBM: energy balance model; GLP-1: glucagon-like peptide 1; PYY: peptide YY

Abstract

A recent Perspective article described the “carbohydrate-insulin model (CIM)” of obesity, asserting that it “better reflects knowledge on the biology of weight control” as compared to what was described as the “dominant energy balance model (EBM)” that fails to consider “biological mechanisms that promote weight gain”. Unfortunately, the Perspective conflated and confused the principle of energy balance, a law of physics which is agnostic as to obesity mechanisms, with the EBM as a theoretical model of obesity that is firmly based on biology. In doing so, the authors presented a false choice between the CIM and a caricature of the EBM that does not reflect modern obesity science. Here, we present a more accurate description of the EBM where the brain is the primary organ responsible for body weight regulation operating primarily below our conscious awareness via complex endocrine, metabolic, and nervous system signals to control food intake in response to environmental influences as well as the body’s energy needs. We also describe the recent history of the CIM and show how the latest “most comprehensive formulation” abandons a formerly central feature that required fat accumulation in adipose tissue to be the primary driver of positive energy balance. As such, the new CIM may be considered a special case of the more comprehensive EBM but with a narrower focus on high dietary glycemic load as the primary factor responsible for common obesity. We review data from a wide variety of studies that address the validity of each model and demonstrate that the EBM is a more robust theory of obesity than the CIM.

Key words: Obesity; Food Intake; Energy Balance; Carbohydrates; Insulin;

Introduction

Theoretical models of the pathogenesis of obesity can help organize and synthesize observations to form hypotheses for experimental interrogation. The results of such experiments can be used to refine or refute models, thereby leading to a better understanding of the mechanistic drivers of common obesity. Therefore, an evidence-based model that increases our understanding of the factors responsible for obesity can be used to design more effective interventions for obesity prevention and therapy.

Two important questions regarding human obesity should be addressed by a successful model. First, what explains between-person variability in adiposity in a population? Second, what explains the global shifts in the population prevalence of obesity over the past several decades? As a partial answer to the first question, body mass index (BMI) is highly heritable and genetic differences explain ~75% of BMI variability among individuals (1, 2). Regarding the second question, while changes in occupational physical activity and the built environment may have contributed to obesity by reducing overall physical activity (3), changes in the food environment are likely the primary driver of the increased obesity prevalence in recent decades (4). However, the specific aspects of the food environment that are most “obesogenic” and how they interact with genetically susceptible individuals to cause obesity are topics that are hotly debated and competing theoretical models implicate different mechanisms.

A recent Perspective article described the theoretical “carbohydrate-insulin model (CIM)” of obesity, asserting that it “better reflects knowledge on the biology of weight control” as compared to what they described as the “dominant energy balance model (EBM)” that was claimed to conceptualize obesity “without considering the biological mechanisms promoting weight gain” (5). In doing so, the authors presented a false choice between the CIM and a caricature of the EBM as theory of obesity that does not reflect modern obesity science.

Indeed, the recent Perspective conflated and confused the principle of energy balance, a law of physics which is agnostic as to obesity mechanisms, with the EBM as a theoretical model of obesity. The Perspective described the EBM as an “inherent tautology” that “considers all calories to be metabolically alike for all practical purposes” (5). These statements more aptly refer to the law of physics and not the EBM as a theoretical model that is firmly based on biological mechanisms. To be clear, all theoretical models of obesity, including the CIM, must satisfy the principle of energy balance to avoid violating the laws of physics.

The Perspective also described a straw-man version of the theoretical EBM postulating that “energy-dense, tasty, modern processed foods drive a positive energy balance through increased intake” under “conscious control” (5). However, this is an inaccurate description of the EBM which we clarify below. We also describe the recent history of the CIM and show how its latest “most comprehensive formulation” (5) constitutes abandonment of its formerly central feature (6-9) and can now be considered as a special case of the EBM that focuses on high dietary glycemic load diets as the primary factor responsible for obesity. We review data from a wide variety of studies that address the validity of each model and demonstrate that the EBM is a more robust theory of obesity than the CIM.

The Energy Balance Model of Obesity

The EBM proposes that the brain is the primary organ responsible for body weight regulation via complex endocrine, metabolic, and nervous system signals to control food intake (**Figure 1**) (10). Specific brain regions, such as the hypothalamus, basal ganglia, and the brainstem modulate food intake below our conscious awareness via complex endocrine, metabolic, and nervous system signals (11-13) acting in response to environmental influences as well as the body’s dynamic energy needs (14, 15). The orchestration of energy homeostasis occurs through short-term signals (e.g., ghrelin, PYY, GLP-1, vagal afferents) controlling meal patterns (i.e., the initiation and cessation of feeding) and long-term signals

(e.g., leptin) that modulate the activity of the short-term system thereby increasing or decreasing overall energy intake. Thus, while day to day energy intake and energy balance of an individual can be highly variable, neural regulation of energy balance is generally achieved over prolonged time scales (16-19).

The EBM proposes that the increasing population prevalence of obesity in recent decades is primarily due to changes in the food environment, including increased availability and marketing of a wide variety of inexpensive, convenient, energy-dense, ultra-processed foods that are high in portion size, fat, sugar, and low in protein and fiber. The CIM Perspective downplayed the potential role of conscious “liking” or palatability of food in driving obesity (5). However, palatability is only one dimension of the multi-faceted concept of food reward that involves incentive salience, wanting, and motivation that primarily operate below our conscious awareness (11).

Brain circuits controlling energy intake respond to a changing food environment in ways that are beginning to be elucidated, especially in mouse models (20, 21). For example, a bidirectional circuit was recently identified between hypothalamic neurons expressing agouti-related peptide (AgRP) that control homeostatic hunger and the midbrain dopamine system influencing food reward (22). Exposure to a high fat diet alters the activity of this bidirectional circuit and results in excess energy intake, development of obesity, and devaluation of a low-fat diet that does not induce obesity (23). Distinct gut-brain pathways have been identified for sensing dietary fat and carbohydrate thereby modulating hypothalamic AgRP neuronal activity (24) and striatal dopamine release (11). Therefore, the EBM is consistent with the idea that diet composition, not simply its caloric content, may be an important factor in the central nervous system control of food intake.

The physical principle of energy balance does not specify the biological mechanisms determining how energy imbalances are partitioned within the body to result primarily in changes in adipose tissue fat stores versus changes in energy stored or utilized in other body compartments – a fact that has been recently misinterpreted as being a deficiency in the EBM (25). However, based on extensive studies of

human macronutrient balance in response to various dietary interventions (26-34), the EBM incorporates physiological mechanisms underlying energy partitioning whereby diet composition and amount affect whole-body net oxidation rates of carbohydrate, fat, and protein such that overall energy imbalances are primarily reflected as fat imbalances regardless of the composition of the diet (35-37). This regulation of macronutrient metabolism is the consequence of coordinated control of multi-organ metabolic fluxes by a variety of hormones, including but not limited to insulin, such that whole body fat imbalances end up primarily reflected as changes in adipose tissue fat storage (38-40). The EBM therefore conceptualizes adipose tissue as an active endocrine organ coordinating the efficient storage and mobilization of energy (i.e., triglycerides) in response to energy surplus and deficit, respectively.

The EBM recognizes that individual differences in energy partitioning can result in different degrees of adiposity, even when energy intake is not different (41, 42). This may happen, in part, because accretion of lean body mass results in greater energy expenditure as compared to accumulation of body fat mass. Indeed, energy partitioning differences explain why females accumulate greater body fat than males during growth and development despite consuming fewer total calories (43) and fat mass may be relatively constant or even decrease during periods of rapid growth where positive energy balance corresponds to increasing lean body mass (44). Furthermore, subtle differences in adipose tissue dynamics may affect energy partitioning and fuel utilization thereby influencing body composition over the long term (45-49), but the extent of such influences on common obesity are currently unclear.

The EBM allows for a role of decreased physical activity in the development of obesity, although not necessarily because of decreased energy expenditure per se but rather due to decreased precision of energy intake control (3, 50, 51). Furthermore, other factors may also play a role in the development of obesity within the EBM framework (52).

The above description of the EBM is inconsistent with the characterization by Ludwig et al. in their Perspective (5) and elsewhere (7) as a theoretical model that “essentially disregards knowledge

about the biological influences on fat storage” proposing that obesity results from “conscious control” of behaviors affecting energy intake or expenditure. Indeed, the EBM emphasizes that powerful internal and external signals influence the neural regulation of energy balance below our conscious awareness and explains why simple advice to “eat less and move more” is ineffective for sustained weight loss.

The Carbohydrate Insulin Model of Obesity

The CIM presented in the recent Perspective (5) is substantially different from its previous iterations (6-9). **Box 1** provides a brief history of related theoretical concepts leading to Taubes’ 2007 proposal of the adipo-centric CIM whereby obesity results from increased dietary carbohydrates driving excess insulin secretion thereby causing adipose tissue to accumulate and trap fat thereby starving non-adipose tissues of fuel (9). Thus, “by driving fat accumulation, carbohydrates also increase hunger and decrease the amount of energy we expend in metabolism and physical activity” (9) and thereby results in positive energy balance with energy intake exceeding expenditure.

Taubes justified his adipo-centric CIM by asserting that “by the mid-1960s four facts had been presumably established: 1) carbohydrates are *singularly responsible* for prompting insulin secretion; 2) insulin is *singularly responsible* for inducing fat accumulation; 3) dietary carbohydrates *are required* for excess fat accumulation; and 4) both Type 2 diabetics and the obese have abnormally elevated levels of circulating insulin” [emphasis added] (9). To explain the epidemiological observations of “the emergence of obesity in recently Westernized populations” Taubes stated that, “carbohydrates...are the prime suspects in chronic elevation of insulin; hence, they are the ultimate cause of common obesity” (9).

Unfortunately, the foundational “facts” of the adipo-centric CIM are in error, particularly the claims of singularity and necessity about the roles of insulin and dietary carbohydrates on adipose tissue fat metabolism. Rather, adipose fat storage can occur in the absence of either dietary carbohydrate or an increase in insulin above basal levels (38, 53, 54). Thus, alternative physiological mechanisms allow

body fat to be stored without the necessity of dietary carbohydrates – a feature of adipose tissue that likely had evolutionary advantages for omnivorous species. Furthermore, insulin secretion is determined by a variety of factors beyond dietary carbohydrate (55-57). Indeed, basal insulin levels are similarly affected by overall energy imbalance regardless of whether the imbalance is achieved by manipulating dietary carbohydrates or fat (58). Thus, there are potentially many paths to fat accumulation and it is not an “inescapable conclusion” as claimed by Taubes that “by stimulating insulin secretion, carbohydrates make us fat and cause obesity” (9).

Despite problems with the foundational logic of the adipo-centric CIM, it was adopted more widely (6-8) with an emphasis that this “model considers fat cells as central to the etiology of obesity” such that “a high-carbohydrate diet...produces postprandial hyperinsulinemia, promotes deposition of calories in fat cells instead of oxidation in lean tissues, and thereby predisposes to weight gain through increased hunger, slowing metabolic rate, or both” (7). Accordingly, a popular diet book based on the adipo-centric CIM claimed that insulin acts as “the ultimate fat cell fertilizer” that “ushers calories into fat cells, but restricts their passage back out”, and consequently “our fat cells make us overeat.” (6). Based on observations that insulin rapidly responds to changes in dietary carbohydrate and has expeditious effects on adipose tissue, readers were advised that “decreasing carbohydrate is the quickest and easiest way to lower insulin and jump-start weight loss” and low carbohydrate diets result in “big declines in hunger, sometimes as early as day 1” (6).

Precisely how carbohydrate-driven insulin action on adipose tissue drives hunger or slows metabolic rate is not specified by the CIM, but low levels of circulating fuels in the late postprandial period after high versus low glycemic load meals have been proposed to be either sensed directly by the brain or via decreased energy status of peripheral organs like the liver. Of course, dips in blood glucose may increase hunger by mechanisms independent of those proposed by the CIM as described long ago in the glucostatic theories of Mayer (59, 60), LeMagnen (61), and Campfield (62, 63). Indeed, greater

dips in blood glucose occurring 2-3 hours after meals were recently associated with increased appetite in humans, although such glucose dips were nominally greater following higher fat versus higher carbohydrate mixed meals (64).

The adipo-centric CIM was expanded beyond dietary carbohydrates and a “comprehensive paradigm” was proposed whereby all obesogenic factors (e.g., amount of dietary protein, micronutrients, poor sleep, stress, physical inactivity, and environmental endocrine disrupting chemicals) “affect insulin secretion or adipocyte biology directly” with increased energy intake and decreased energy expenditure as necessary downstream consequences (7). Hence, the adipo-centric CIM achieves the much-touted reversal of the direction of causation whereby “positive energy balance does not cause increasing adiposity; rather, a shift in substrate partitioning favoring fat storage drives a positive energy balance” (5).

Abandonment of the adipo-centric carbohydrate insulin model

Some of us (JRS and KDH) recently argued against the adipo-centric CIM and suggested that insulin and other factors exert pleiotropic actions on a variety of organs that influence energy balance (10). Interestingly, the latest formulation of the CIM (5) also de-emphasizes the formerly central role of adipose tissue and thereby abandons the “comprehensive paradigm” of the adipo-centric CIM (7). The new CIM “considers that substrate partitioning and fat deposition are determined by the integrated actions of insulin, together with other hormones and autonomic inputs, in multiple organs, not just adipose tissue” (5). Unfortunately, the proposed mechanisms involved in this integrated, multi-organ, multi-hormone CIM remain unclear, including the mechanisms of “internal starvation” of non-adipose tissue and how this is sensed during the development of obesity.

Importantly, despite continued claims that the new “CIM proposes a reversal of causal direction” (5), this is no longer a necessary feature because all pathways to positive energy balance are

not required to act downstream of adipose tissue fat accumulation. Indeed, the new CIM proposes the existence of parallel pathways influencing energy balance, but it is unclear exactly what these pathways are or how they might work. One such pathway involves a direct effect of dietary glycemic load on energy intake, presumably mediated by the brain (5). If this new pathway from high glycemic load diets to directly increase energy intake dominates the proposed indirect effect downstream of adipose tissue, then the new CIM results in the usual causal direction of increased energy intake leading to adipose tissue fat accumulation. In that case, the new CIM may be considered an oversimplified version of the EBM with a focus on glycemic load as the main driver of excess energy intake.

Evaluation of the EBM and CIM

While data may support various aspects of both the EBM and CIM, a valid model should withstand tests of its various predictions or be suitably modified or abandoned. Most importantly, theoretical models of obesity must explain between-person variability in adiposity as well as the recent global shift in its distribution. Below, we describe a wide body of evidence with implications for the validity of the CIM and EBM as plausible models that explain the heterogeneity of adiposity and the obesity pandemic.

Rodent studies

Rodent models are valuable for testing hypotheses of diet and body weight regulation because they are amenable to rigorous control of diet for extended periods and independent of potentially confounding factors such as the conscious desire to lose weight. Moreover, responses of different strains to variable macronutrients in the diet may provide insights into the regulatory systems involved. However, the high level of control comes at the cost of questionable translational relevance to human obesity (10). For example, rodent studies have been critical in demonstrating the causal role of insulin

affecting aspects of metabolism, food intake, and fat deposition (65-71); however, this evidence does not discriminate between EBM and CIM because both models recognize the importance of these processes (10).

Conversely, other studies show that the role of dietary carbohydrates in determining body weight, as postulated by the CIM, is largely untenable. Most standard laboratory rodent diets are high in carbohydrates. Typical mouse 'chow' consists of around 70% carbohydrate, 10% fat, and 20% protein (by energy) which does not induce obesity. Shifts in the macronutrient distribution towards *lower* percent carbohydrate and *higher* percent fat, with protein constant, induces obesity in many strains, with a peak effect on body fatness observed at 20% carbohydrate, 60% fat, and 20% protein (72, 73). Although it has been argued that this is because the carbohydrates in such diets are not high glycemic index carbohydrates (74), this is incorrect. The main carbohydrate components of commercial mouse chow are corn starch, maltodextrin, and sucrose (75), which all have roughly equivalent glycemic indices in rodents (76). Even if one focuses on sucrose alone, feeding mice a diet with 73% calories as sucrose (82% of calories as carbohydrates, 8% as fat and 10% as protein) was protective against obesity (77), consistent with the lower body weight gain of rats on a 51.3% glucose diet (by weight) (74). Alternative explanations for these findings include potential confounding by higher intakes of saturated fatty acids by rodents fed low glycemic index diets, such that saturated fats induce insulin resistance, hyperinsulinemia, and subsequent obesity (5, 74). As such, this argument underscores the importance of dietary factors other than carbohydrate per se in the pathogenesis of obesity, emphasizes the ability of some strains to resist diet induced changes in fat storage, and directly refutes the notion that dietary carbohydrate is the main driver of body accumulation as proposed by the CIM.

Human genetics

The EBM implicates the brain as the primary organ responsible for obesity whereas the CIM implicates adipose tissue. Given the high heritability of obesity, the relative expression of common obesity genes in different organs provides evidence regarding the relative validity of these models. Other than rare mutations in the leptin gene that result in obesity due to the inability of the brain to sense adequate body fat stores, no genetic disorder primarily affecting the adipocyte or enhanced insulin action has been reproducibly reported to cause obesity. Humans who have homozygous mutations in ATGL or CGI58 have a severe defect in adipocyte lipolysis yet do not develop obesity (78, 79). Nevertheless, adipose enriched genes include variants influencing body fat distribution and features of the metabolic syndrome, such as insulin resistance (80).

Given that nervous systems have evolved to control energy intake (81), it is not surprising that every known monogenic disorder that causes human obesity involves a gene intimately involved in the control of energy intake by the hypothalamus (82). Furthermore, unbiased genome-wide association and gene expression studies have determined that variations in total adiposity between people are primarily due to differences in genes that are most highly expressed in the brain (82-84). The case of common variants, their effects on fat mass are so small that it is hard to definitively establish the impact of each individual variant on food intake, energy expenditure, or energy partitioning. An exception is the common variant with highest effect size, FTO, where carriers of the risk allele have consistently been reported to have increased appetite and/or objectively measured food intake (85, 86).

Epidemiological studies

There is heterogeneity both in the mean BMI among regions globally, by sex, and national income, and in BMI trends observed from 1980 to 2008 (87). The worldwide obesity epidemic has been

attributed in large part to shifting towards industrialized Western diets (88, 89), characterized by refined grains, processed oils, sugar-sweetened beverages, animal products, and low intakes of non-starchy vegetables and whole grains. Global trade and improved technologies have facilitated the rapid dissemination of food commodities both intentionally, to address crises of under-nutrition, and via stealth expansion of the food industry (88-91). These have led to declines in whole grains, vegetables, and legumes, replaced by increases in caloric sweeteners and refined oils in the form of processed foods.

Despite such notable shifts in diet quality, US trends of average adult food intake indicate a remarkable stability in the macronutrient composition of calories from carbohydrate, fat, and protein (92). Further, while added sugar from foods has also been stable, its intake from beverages underwent a significant increase in the first half of the obesity epidemic (93). Since around 2000, modest improvements in diet quality have been observed, such as substituting from refined back to whole grains and a reduction in sugary beverages (94).

Global validated physical activity data are sparse relative to nutrition. There was an increase in the portion of the global population living in urban vs. rural areas, from 41% to 55% over 1985 to 2014 (95), suggesting a role for a sedentary lifestyle in obesity; however, an analysis from the NCD Risk Factor Collaboration (NCD-RisC) indicated many countries experienced greater increases in BMI in rural rather than urban areas, suggesting trends in urbanization alone are insufficient to explain global obesity trends (96).

Overall, the accumulated trend data implicate a myriad of potential drivers of weight gain accompanying complex global nutrition, economic, and technological transitions (97). Their relative causal contributions, however, cannot be inferred on the population level. Nonetheless, evidence to suggest carbohydrate intake explains between-country differences in body weight are non-existent and recent trends do not support that dietary carbohydrate is the main driver of the US obesity epidemic.

Longitudinal cohort data has similarly identified several potential nutritional risk factors well-beyond simple macronutrient composition for midlife weight gain. For example, an analysis of 121,335 healthy US adults related individual-level changes in dietary fats vs. carbohydrates with concomitant changes in body weight over 20-years of follow-up (98). Participants increasing calories from total fat at the expense of carbohydrate had modestly less weight gain over time, supporting a potential role for carbohydrate reduction in mitigating increases in weight gain in middle age. However, when the *type of fat* replacing the carbohydrate calories was considered, it was clear that changes in the quality of foods contributing dietary fat explained significant differences in weight gain above and beyond any contribution from a reduction in carbohydrate calories *per se*. A reduction in carbohydrates with increases in animal source fats was associated with significantly greater weight gain, while the same reduction in carbohydrates with increases in polyunsaturated fats was correlated with significantly less weight gain.

A large body of epidemiologic evidence consistently finds meaningful differences in risk of overweight and obesity according to long-term adherence to a variety of healthful dietary patterns (99) and foods (100, 101), all with highly variable carbohydrate contents. For example, increasing intake of potato chips, unprocessed red meat, and sugary beverages were significantly related to midlife weight gain, while increases in servings of whole grains, yogurt, and nuts related to weight loss (102). Thus, in addition to genetic factors, heterogeneity in weight gain is explained by variation in several nutritional factors and diet quality, independent of carbohydrate and glycemic index (103, 104). These data, consistent with the EBM, suggest a variety of potential dietary drivers of excess calorie intake but do not support the CIM proposition that dietary carbohydrates are the primary driver of obesity.

Human diet intervention studies

The CIM predicts that meaningful long-term weight loss is readily achieved through a reduction in dietary carbohydrate and glycemic load because such interventions directly address the fundamental cause of obesity and should thereby facilitate its reversal. Indeed, the CIM claims that “patients may experience less hunger and improved energy level, promoting spontaneous weight loss”, and “weight reduction produced by carbohydrate restriction would...result in lower spontaneous food intake” (5).

However, diet intervention trials have found that low glycemic load diets do not generally result in significantly greater long-term weight loss as compared to higher glycemic load diets (105-112). Furthermore, maintenance of lost weight six months after losing weight on a low-calorie diet was only achieved using a high protein, low glycemic index diet but not using a lower protein, low glycemic index diet or higher glycemic index diets with high or low protein (113). Therefore, dietary protein can be a significant confounder in diet intervention studies and should be matched when evaluating the effects of glycemic load per se. Interestingly, longer studies investigating maintenance of lost weight failed to show a benefit of low versus high glycemic index diets (114, 115). Furthermore, a meta-analysis of 53 randomized controlled trials of 1-year duration or longer evaluated the effects of low-fat vs. higher fat dietary interventions and found no significant difference in mean weight loss comparing the low-fat vs. higher fat diets when dietary interventions were delivered with similar intensity (116). An updated network meta-analysis of 121 RCTs found no significant difference in mean weight loss at 6 months comparing low-fat, low-carbohydrate, or moderate-carbohydrate vs. usual diet controls (117). For the individual diet types, Jenny Craig (55-60% carbohydrate) and Atkins (~10% carbohydrate) were the most effective at 6 months; however, at 12 months mean weight loss was significantly greater for Jenny Craig vs. Atkins.

The CIM Perspective admitted that “most participants in these studies have difficulty sustaining dietary change” (5), but this explanation is contrary to predictions of the CIM because low glycemic load diets should promote diet adherence in comparison to higher glycemic load alternatives because they are postulated to spontaneously decrease hunger. In contrast, the EBM predicts that a variety of macronutrient compositions and eating patterns can result in long-term weight loss, so long as they ultimately confer a sustained reduction in energy intake. The EBM is not constrained by the degree of effort necessary to sustain adherence across diet types, and readily accommodates a direct influence of internal signals and the complex and dynamic food environment on the long-term control of energy intake that make it difficult to sustain dietary adherence (118-120).

To avoid the confounder of diet adherence, inpatient feeding studies prevent access to off-study food. Under such conditions, exposure to a high glycemic load diet is predicted by the CIM to lead to excess insulin secretion, accumulation of body fat, and downstream increases in appetite leading to greater *ad libitum* energy intake as compared to a lower glycemic load diet. However, a recent month-long inpatient study found that two weeks of exposure to a high glycemic load diet resulted in ~700 kcal/d lower *ad libitum* energy intake and body fat loss compared to the two weeks spent by the same participants on a very low glycemic load diet (121). Additionally, these results occurred despite the low glycemic load diet resulting in substantially lower insulin secretion. Although this study provides important evidence directly contradicting the CIM’s predictions, it was wholly dismissed in the CIM Perspective as an example of “the pitfalls of extrapolating chronic macronutrient effects from studies of a few weeks’ duration” when the effects of the high glycemic load diet and excess postprandial insulin on appetite were apparently dominated by “factors of dubious relation to chronic energy balance—such as utensil size or plate color” (5). Interestingly, a recent outpatient controlled feeding study found that 10 to 15 weeks of a high-carbohydrate diet significantly *increased* satiety compared with a low

carbohydrate diet despite resulting in significantly higher postprandial insulin and lower circulating fuels (122) which again refutes the CIM predictions and is consistent with the shorter inpatient study (121).

The CIM predicts that lower carbohydrate diets decrease insulin and thereby mobilize fat from adipose tissue to result in greater fat loss compared to isocaloric higher carbohydrate diets with matched protein. However, controlled feeding studies have produced results inconsistent with this prediction. For example, selective carbohydrate restriction led to substantial decreases in daily insulin secretion in patients with obesity but resulted in slightly *less* body fat loss compared with isocaloric selective fat restriction in the same patients (58). A meta-analysis of controlled feeding studies comparing isocaloric diets matched for protein found a small but significantly *greater* body fat loss with higher carbohydrate diets (123). Furthermore, a recent six-week controlled feeding study found no significant differences in body fat loss between isocaloric very low carbohydrate versus low fat diets matched for protein (124). Finally, a 17-week controlled feeding study employing isocaloric diets varying in glycemic load but matched for protein also failed to observe significant differences in body fat loss (109).

The EBM proposes that high dietary energy density is a potentially important driver of excess energy intake, and several trials have demonstrated significant long-term effects of diets differing in energy density (125-128). However, these data were ignored in the CIM Perspective and the possibility of energy density being potentially important in long-term control of energy intake was rejected (5) on the basis of a single exploratory finding of no significant long-term weight loss in patients with breast cancer who were advised to eat more fruits and vegetables (129). Furthermore, the CIM Perspective conflated the concept of food palatability with ultra-processed food, and it was claimed that there is a lack of relevant human intervention studies on the topic (5). But this ignored the results of a month-long inpatient human trial demonstrating excess *ad libitum* energy intake and weight gain when people were exposed to controlled food environments characterized by either ultra-processed or unprocessed diets

rated as similarly palatable and closely matched for available energy, macronutrients, sugar, sodium, fiber, and glycemic load (130). Such results demonstrate that factors other than dietary macronutrient composition and glycemic load may play important roles influencing human energy intake.

Human pharmacological intervention studies

Pharmacological manipulations can also be used to interrogate the validity of obesity models. An oft cited example in support of the CIM is that exogenous insulin treatment in people with diabetes often induces weight gain. But insulin therapy in treatment-naïve patients with type 1 diabetes normalizes their pathophysiological catabolic state and results in increased lean mass, reductions in ATP-requiring metabolic futile cycles, normalization of adipose tissue lipolysis, elimination of glycosuria and, contrary to the CIM, resolution of polyphagia. Further, this all occurs despite insulin therapy decreasing circulating fuels. In type 2 diabetes, weight gain with insulin therapy may be due, in part, to regain of recently lost weight (131-133). Acute peripheral infusions of insulin have mixed effects on appetite and food intake in humans (134, 135), but intranasal insulin delivery to the brain inhibits food intake (136), consistent with rodent studies (137) and contrary to the CIM.

The CIM posits that a major reason why insulin induces weight gain is due to its effect on inhibiting adipose tissue lipolysis thereby trapping fat in fat cells (5). However, inhibiting adipose lipolysis with acipimox treatment for six months had no significant effects on energy intake, resting energy expenditure, or body composition despite achieving a marked 38% reduction of plasma FFA levels in adults with obesity (138). Finally, despite acutely increasing insulin secretion, GLP-1 receptor agonists are currently the most effective approved medications to treat obesity (139).

Conclusions

The principle of energy balance is a necessary constraint on all potentially viable models of obesity, including the CIM and EBM. Both models agree that diet quality and composition are important in prevention and treatment of obesity. Both models account for endocrine regulation, peripheral energy sensing, and energy partitioning. The latest iteration of the CIM retreats from its previous focus on postprandial insulin's direct effect on adipose tissue, but the new CIM differs from the EBM in that high glycemic load diets are identified as the main driver of increasing obesity prevalence. However, an overwhelming amount of evidence indicates that numerous variables in the food environment beyond high glycemic foods can result in increased energy intake and the EBM posits that obesity can arise if any one or more of these factors are in play.

The EBM acknowledges the potential benefits of low carbohydrate or low glycemic load diets in managing body weight or cardiometabolic outcomes in some individuals. Precision nutrition initiatives have stemmed from a hypothesis of inherent biological heterogeneity when optimizing individuals' diet (108, 140-142). While such efforts are consistent with the multifactorial EBM, the CIM sets forth one exposure as the primary determinant of common obesity and proposes a single "practical strategy" to treat obesity by prescribing low glycemic load diets (5) despite evidence that such interventions are no more effective than prescribing higher glycemic load alternatives (105-112, 114, 115).

Overall, we have documented a large body of evidence aligning with the EBM but inconsistent with the CIM. Further development of the EBM requires elucidation of the factors in the dynamic food environment that are most responsible for instigating obesity, the mechanisms by which these factors alter the brain circuits controlling food intake, and why some individuals are more susceptible to development of obesity than others. Answering these questions will result improved public health and medical interventions for prevention and treatment of obesity.

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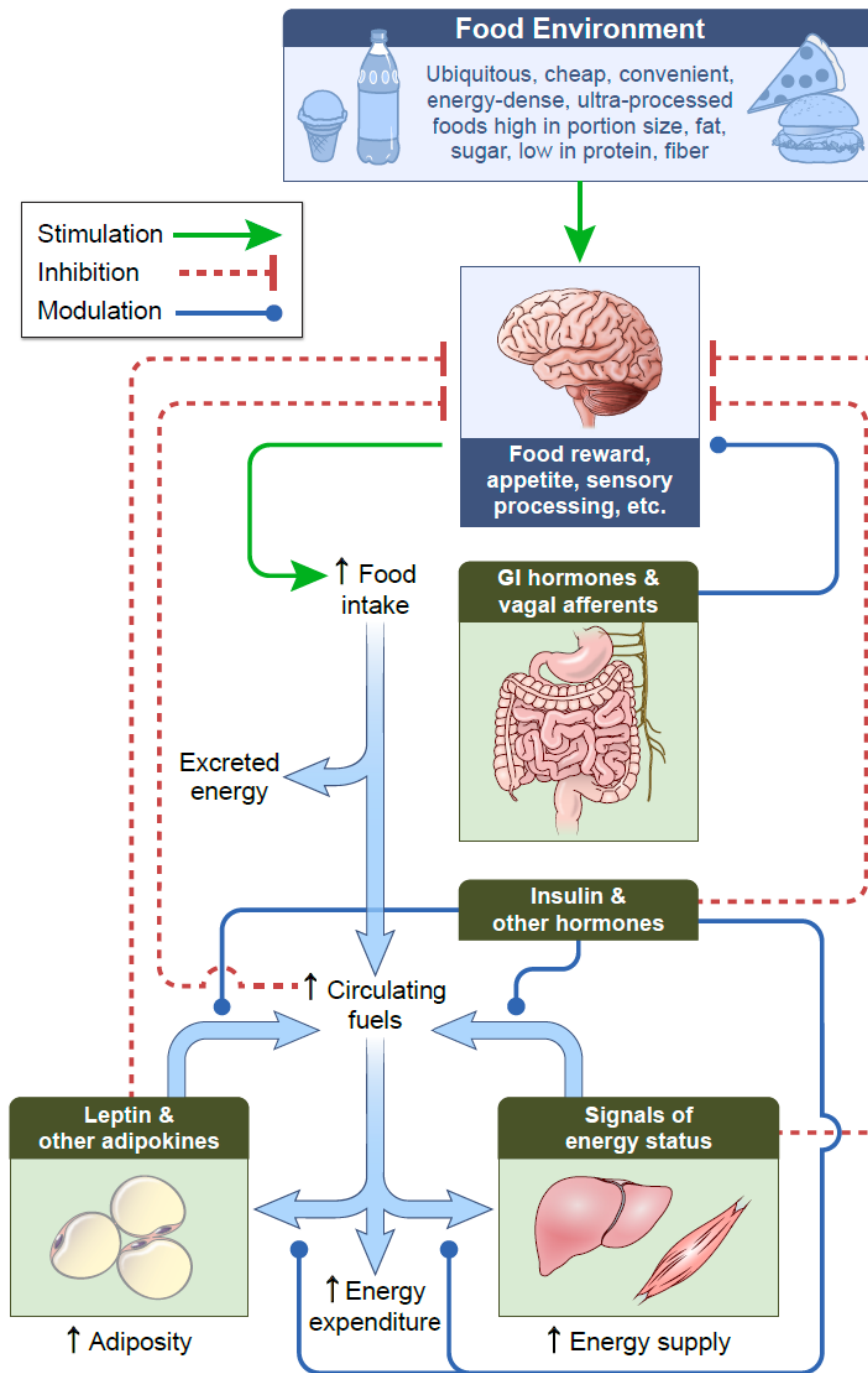


Figure 1. The Energy Balance Model of Obesity posits that body weight is regulated by the brain in response to external signals from the food environment that are integrated with internal signals to control food intake below our conscious awareness. Increased prevalence of obesity has resulted from

changes in the food environment leading to increased food intake and circulating fuels. Hormones, including insulin, respond to the intake and absorption of nutrients to direct the flow of metabolic fluxes into and out of various organs and provide signals to the brain that control food intake. Energy supply to organs such as liver and muscle increases, which supports their increased growth during the development of obesity and may result in ectopic lipid accumulation. Signals indicating the energy status of various organs are sensed by the brain to control food intake by mechanisms that remain to be fully elucidated. Oxidation of carbohydrate, fat, and protein provides the body with its energy needs which increase as obesity develops. Adaptations of metabolic fuel selection as well as changes in endocrine milieu ensure that partitioning of overall energy imbalances are primarily reflected as changes adipose tissue triglyceride storage regardless of diet composition. Inherited variation in the operation of these processes, particularly those in the brain, are responsible for a substantial proportion of the inter-individual difference in susceptibility or resistance to developing obesity in a particular environment. Thick blue arrows indicate the flow of energy.

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Box 1: Historical antecedents of the adipo-centric CIM

In the early 20th century, the idea of “lipophilia” proposed adipose tissue was the primary site of dysregulation in obesity, although dietary carbohydrate-driven insulin secretion was not implicated in this pathophysiology (143). In the early 1950s, Pennington proposed that people with obesity have a cellular defect in their ability to oxidize carbohydrate that resulted in increased *de novo* lipogenesis, suppression of adipose lipolysis, and thereby resulted in body fat accumulation along with reduced energy expenditure and increased appetite (144-148). While such a cellular defect was never found, Pennington speculated that dietary carbohydrate-driven insulin secretion exacerbated the problem which helped explain the apparent effectiveness of his low carbohydrate diet regimen for treating obesity. In 1962, Astwood expanded on the lipophilia concept by hypothesizing that increased appetite in some people with obesity may be due to aberrant action of insulin, cortisol, or other hormones to either trap fat in adipose tissue or prevent fat oxidation in peripheral tissues (149). Beginning in the mid-1970s and extending into the late 1990s, Mark Friedman proposed that energy sensing in peripheral tissues, especially the liver, provides the primary signals to the brain controlling energy intake (150-153) and noted that diets high in both fat and carbohydrate may be responsible for obesity due to aberrant fuel partitioning to adipose tissue leading to a decrement in liver energy status (150).

In the early 2000s, Ludwig hypothesized that overeating is the result of consuming high glycemic index foods that rapidly increase plasma glucose and insulin, resulting in uptake of nutrients in insulin responsive tissues and subsequent decreases in circulating fuels in the late-postprandial period that are sensed by the brain to promote hunger (75, 154). In 2006, Lustig linked increasing population obesity prevalence to “our current Western diet [that] is highly insulinogenic, as demonstrated by its increased energy density, high fat content, high glycemic index, increased fructose composition, decreased fiber,

and decreased dairy content” (155). Lustig proposed that autonomic dysfunction potentiates diet-induced hyperinsulinemia which was hypothesized to increase energy intake by antagonizing leptin signaling and increasing dopamine in the brain. Neither Ludwig nor Lustig emphasized a central role of adipose tissue insulin signaling in their models of obesity. Rather, insulin was presumed to act on multiple organs in parallel, and the brain played a direct role in controlling energy intake either by sensing low levels of circulating fuels (75) or by altered central leptin and dopamine signaling as a result of hyperinsulinemia (155).

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