Physiology of Food Intake Regulation: Interaction with Dietary Components

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Abstract

Food intake is regulated in both the short- and long-term by a complex physiological system that involves neuroendocrine pathways that are both distinct and overlapping. The underlying causes and mechanisms of the dysregulation of food intake in obesity is poorly understood; however, it is clear that dietary components interact with the physiological determinants of food intake and can cause profound alterations during the development of control mechanisms. The objective of this review is to discuss possible food solutions to the obesity epidemic based on our current understanding of food intake regulation and its interaction with dietary components. First, the physiology of long- and short-term food intake regulation is reviewed. The effects of dietary components on food intake, satiety and intake regulatory markers are then discussed with particular emphasis on macronutrient class and source. Finally, the impact of nutritional manipulations during the early stages of development on food intake and metabolic regulation is examined, followed by a brief description of the possible genetic and epigenetic mechanisms involved.

Introduction

Food intake is controlled by an extraordinarily complex system. The urgency to understand the system is obvious in order to determine how physiology might contribute, or be harnessed, to reverse the current epidemic of obesity. Progress is being made in understanding the complexity of the system, but it is clear that evolution has built in sufficient room for conservation of energy so that in an environment of plentiful food and limited activity the majority of individuals accumulate excess energy.
A genetic or pharmacologic solution does not appear likely in the near future. Although more than 600 genes that play a role in obesity and its disorders have been identified [1], a fundamental change in the genome would not have occurred concurrently with the increase in obesity over the past 30 years. In addition, the connectivity and integration of brain and peripheral circuits associated with feeding is characterized by redundancy. That is, the feeding circuit can rearrange itself even if one of the components of the system is removed or enhanced [2], suggesting that a single and safe drug solution might be unlikely for either prevention or treatment of obesity.

Of some certainty, however, is the fact that the interaction of genes with lifestyle and the food supply is a strong contributor to the obesity epidemic. There is very limited understanding, yet, of how environmental factors affect the development and function of physiological mechanisms of food intake control [3]. Thus, it is unclear whether obesity and its associated disorders develop in susceptible individuals because the physiological mechanisms of food intake control are compromised first, beginning in utero, or if they are simply overridden by the environment and become compromised later. Because the focus of this review is on the physiology of intake regulation, lifestyle will not be considered. Rather the goal is to determine if there is a food solution to intake control. Food triggers multiple physiologic responses that induce satiety, and its components may cause profound alterations during the development of control mechanisms.

The question to be examined is: Arising from the new advances of understanding the circuitry, anatomy, and neurochemical processes involved in intake control, do we have new insights on food characteristics that interact with the intake regulatory system? If not, what might be emerging as a solution?

To encourage a discussion of this question, a background review of the intake regulatory system is provided first, followed by an examination of the interaction of dietary components with intake control mechanisms.

**Physiology of Intake Regulation**

Food intake is regulated in the central nervous system, which receives input from sensory properties of food, mechanical and chemical receptors in the gut, circulating metabolites, and hormones. A complex neuronal circuitry involving the hypothalamus, brainstem and cortex integrates these signals and translates them into information regulating meal size and duration, interval to the next meal, the amount of food consumed over the day or several days, weeks and months, and possibly the composition of food as well as the intake of total energy (fig. 1). The hypothalamus regulates both long-term and short-term intake. The long-term regulation of food intake is mediated by leptin and insulin secreted in proportion to the adipose tissue mass and exerting their action in the hypothalamus [4, 5]. These hormones affect the amount of food...
consumed over the day or several days, weeks and months, body fat energy stores, basal metabolism, thermogenesis and eventually body weight. They have also been shown to act synergistically with gut hormones in the regulation of short-term food intake as well [4], thus emphasizing the intertwining and redundancy of the intake regulatory system.

Energy imbalance could arise from errors in the regulation of many aspects of short-term intake as well as in the long-term monitoring of intake [3]. As described in the following, many physiologic signals have been shown to contribute to short-term intake regulation. At present the relative importance of each of the signals in contributing to satiety is unclear. Furthermore, it is possible that due to plasticity of the regulatory system, a decreased sensitivity to satiety signals occurs during maturation or in adulthood, thus contributing to obesity. Some research has led to the suggestion that compensation for the energy content of preloads consumed before test meals is highly variable among children but less precise in older compared with younger children [6]. Much more research is required to determine the genetic and physiological origins of variability in short-term intake.

**Short-Term Intake Regulation**

Many of the signals that result in a decrease in food intake in the short-term are activated by gastrointestinal (GI) responses to food ingestion and are transmitted to feeding centers in the brain, primarily via the vagus nerve. The interactions between the gut and the food ingested depend on the macronutrient composition of the food. In addition to being populated by receptors that respond to the physiochemical properties of food, the gut has evolved to recognize the composition of the food ingested and to send signals
in anticipation of their metabolic effects by release of peptide hormones to
different organs involved in the processing of the nutrients derived from
digestion and absorption [7]. Whereas long-term food intake is controlled by
adiposity signals, the regulation of short-term food intake is dictated mainly
by food signals arising from both their preabsorptive action in the gut and
their postabsorptive metabolism.

**Preabsorptive Signals**

The ingestion of food and the passage of its subsequent digestion products
through the GI tract prior to absorption gives rise to a myriad of signals that
are transmitted to the brain, primarily by the vagus nerve, and are integrated
with long-term energy signals to ensure an appropriate food intake response
[8]. Mechanoreceptors, osmoreceptors and chemoreceptors in the stomach
and the small intestine provide direct signals to the brain. In addition, nutri-
ents stimulate the release of GI hormones that act directly on receptors in the
vagus nerve and in the brain.

Slower gastric emptying is associated with increased satiety [9]. Many fac-
tors contribute to the rate of emptying, including the physical state and tem-
perature of the meal, volume ingested, osmolality, calorific content, released
digestive products and hormonal interactions. Solid foods are emptied more
slowly from the stomach than liquid, increased volume accelerates the rate of gas-
tric emptying, and solutions of high osmolality slow gastric emptying. However,
while gastric distension contributes to food intake regulation, it alone cannot
explain the state of satiety that typically lasts for several hours after a meal [10].

The secretion of hormones controlling food intake is regulated by the pres-
ence of food in the GI tract. The gut is a source of numerous peptides that con-
tribute to the regulation of intake and metabolism. These include, from the
small intestine, cholecystokinin (CCK), glucagon-like peptides (GLPs) 1 and 2,
bombesin, gastrin-releasing peptide, neuromedin B, glucagon, apolipoprotein
A-IV, amylin, somatostatin, enterostatin and peptide YY (3–36) and from the
stomach, ghrelin and leptin [7, 11]. Many of the GI hormones and/or their recep-
tors are also expressed in the central nervous system, underlining their impor-
tant role in appetite control [11]. Some enter the central circulation via leaky
areas (brainstem and hindbrain) in the blood-brain barrier, or send signals
through vagal afferents that are relayed to the hypothalamus. The macronutri-
ent-dependent release of gut hormones might explain, at least in part, differ-
ences in the satiating and satiety effect of macronutrients. For example, fat and
protein are the main CCK secretagogues in humans and rats, respectively [12],
whereas carbohydrate and fat are stronger stimulants of GLP-1 release [13].

While the emergence of knowledge of the multiple satiety signals arising
from the GI tract adds to the understanding of intake control, it has not yet
led to an integrative picture of the action of these peptide hormones or to an
understanding of their relative importance in response to food ingestion.
Similarly, the role of postabsorptive signals remains unclear.

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Postabsorptive Signals

Postabsorptive signals are generated after nutrients have been digested and have entered the circulation where they stimulate satiety centers in the brain by endocrine and metabolic actions. The glucostatic, aminostatic and lipostatic hypotheses of intake regulation have been the main theories describing how absorbed nutrients generate and influence satiety signals [14].

The glucostatic theory postulates that fluctuations in blood glucose levels trigger an appropriate change in food intake. In support of the hypothesis, transient declines in blood glucose of the correct magnitude and time course have been associated with meal initiation as they are detected by peripheral and central glucoreceptive elements.

Similar to the glucostatic theory, the aminostatic hypothesis is based upon the brain monitoring of nutrients, in this case amino acids derived from protein ingestion, and consequently shaping consumption patterns. An inverse relationship between serum amino acid concentration and appetite in humans has been observed. It has been further postulated that amino acids act on food intake regulation through their ability to act as precursors to certain neurotransmitters known to influence food consumption. But as reviewed elsewhere, this may be a mechanism determining later food selection and the inter-meal interval rather than within meal satiation [15].

The lipostatic theory, advanced over 50 years ago, was based on signals arising from the metabolism of fats. In recent years, new evidence has emerged to support the hypothesis. Transport mechanisms and enzymes for both fat oxidation and synthesis are present in the brain and inhibitors of fatty acid oxidation increase food intake. Although this could be a peripheral effect, it is clear that the hypothalamus senses a nutrient surplus in fatty acid metabolism arising from circulating lipids from either dietary sources or adipose tissue [16].

In addition to glucose, fatty acids and amino acids, a number of intermediate products of metabolism associate with satiety. Ketones, lactate, and pyruvate suppress food intake in animals [8].

Dietary Components and Intake Regulation

Food and its components contribute to both short- and long-term regulation of food intake. The challenge is to understand the relative importance of food components and how to optimize their interaction with intake regulatory systems.

Energy

At the physiological level, energy requirement is a powerful determinant of food intake [14]. Thus growth, increased activity, and exposure to cold increase intake. Physiological systems in both experimental animals and humans are remarkably precise in regulating energy intake in relation to requirements. For example, exposure to cold or to exercise, or alterations in
the energy density of the diet or to food availability and choice result in rats quantitatively adjusting their food intake, thus maintaining energy balance when provided with their usual diets [14, 17]. However, it is also clear that experimental animals will become obese when provided a variety of palatable foods, or high fat diets, showing that factors other than the physiological drive toward energy balance determine food intake [18].

Similarly, humans adjust their energy intake to meet their energy expenditure in response to changes in activity, or ambient temperatures. As with experimental animals, humans consume excess energy when they are exposed to an environment of low activity [19] and highly palatable energy dense foods [20].

Although all macronutrients provide energy, their effect on food intake cannot be predicted simply from their energy content. Each macronutrient possesses unique properties that provide signals to the central nervous system independent of their energy content [14].

**Macronutrients**

Protein suppresses food intake more than carbohydrate, which in turn suppresses food intake more than fat. This hierarchy has been shown in both humans and rats [15]. Less appreciated is that even within a macronutrient class, the source is a factor influencing short-term food intake and appetite. However, it is not possible at present to identify the primary biomarkers of satiety that arise from proteins, carbohydrates and fats.

Proteins

The mechanisms by which proteins stimulate intake regulatory systems are many, making them unique compared with carbohydrates and fats. Furthermore, the systems stimulated are dependent on the source. The satiety cascade arising from protein is as follows. First, protein initiates satiety through its digestion and the subsequent release of biologically active peptides (BAP) encrypted within the protein. These BAP affect feeding through their actions in the GI tract. They activate receptors, thus providing signals via the vagus nerve either directly, or by interacting with gut hormones that are involved in intake regulation. Second, free amino acids arising from digestion activate neurochemical systems, thereby contributing not only to satiety, but also to macronutrient choice. Finally, the end products of amino acid metabolism, ammonia and urea, probably play a part in determining intervals between meals, but act primarily to signal excess intake or errors in metabolism [14].

Protein source, in addition to protein quantity, is a determinant of satiety [15]. Greater subjective satiety was reported by young men fed a 50-gram meal of lean fish compared with an equivalent amount of either beef or chicken [21]. Whey and soy protein drinks (45–50 g protein) suppressed food intake 1 h later compared with the energy-free control and with sucrose, whereas egg albumen did not [22].
The differential effect of protein source on food intake and subjective
appetite might be explained by the action of BAP released during protein
digestion. These peptides are unique to the protein source and dependent on
its tertiary structure and amino acid composition. Among the most exten-
sively studied BAP are those derived from milk digestion. A glycosylated form
of caseinomacropeptide (GMP), a peptide derived from the in vivo and in
vitro digestion of casein, is a potent CCK secretagogue [23], and preliminary
studies from our laboratory show that GMP is a potent inhibitor of food intake
in rats [24]. In addition to GMP, opioid peptides derived from the digestion of
casein (casomorphins) suppress food intake through opioid receptors located
in the GI tract [25].

Carbohydrates
Consistent with the glucostatic hypothesis are the observations that car-
bohydrate consumption and the resulting increase in blood glucose are asso-
ciated with satiety. In the short-term, high glycemic carbohydrates suppress
food intake (up to 2 h) more than low-glycemic carbohydrates [26]. Although
there is much indirect support for the hypothesis that satiety is associated
with the glycemic effects of carbohydrates, a primary role for blood glucose
in determining satiety remains uncertain [27], perhaps because the glycemic
response to carbohydrates primarily depicts their absorption characteristics.
Many other mechanisms, including those based on the rate of gastric empty-
ing and gut hormones, may explain the different effects on satiety of slow
compared to rapidly digested carbohydrates. For example, a rapid increase
in the stimulation of glucoreceptors would be expected following ingestion
and digestion of carbohydrates, but this stimulation does not last long
enough to account for the prolonged satiety effect. A more extended effect of
carbohydrates on satiety could arise from the stimulation of a multitude of
gut peptides, such as GLP-1 and CCK [28, 29]. Gastric emptying is slowed by
GLP-1, a putative satiety peptide whose release is stimulated by carbohy-
drates in the small intestine and that regulates carbohydrate metabolism
[13]. A rise in blood glucose concentrations is also a factor that slows gastric
emptying [30].

Fats
In general, fat suppresses food intake less than carbohydrate or protein on
a calorie for calorie basis. However, this ranking may also depend on the
source. Among fats, both the chain length and the degree of saturation have
been shown to impact short-term food intake and subjective appetite.
Medium-chain triglycerides and polyunsaturated fatty acids suppressed food
intake more than long-chain triglycerides and monounsaturated or saturated
fatty acids, respectively. These effects have been attributed to the CCK and
apolipoprotein A-IV releasing properties of these types of fats [31].
It is clear that an understanding of the interaction between food components and the intake regulatory mechanisms continues to develop. However, as noted earlier, there is little information on the stability of the system once the development of the circuitry has been completed. Similarly lacking is information on the role of environmental or nutritional factors in the development of the intake regulatory system in utero and in early life.

**Nutrients and Development of Intake Control Mechanisms**

Although it is clear that increased risk of chronic disease and obesity are associated with exposure to both deficiencies and excesses of energy and nutrients in utero and in early life [32], there has been very little examination of the role of nutrients in the development of food intake regulatory mechanisms in the etiology of metabolic disease. As with many physiological systems, the development of intake control mechanisms would be expected to occur both in utero and in the early life of the offspring.

The interaction among nutrients and development of regulatory systems in determining effects in later life is complex and there are likely multiple mechanisms to explain the outcome. Altered gene expression is a likely factor. In addition, the development of regulatory systems in the GI tract continues after birth and depending on the composition of the food may have long-lasting effects.

Altered expression of genes regulating insulin has been offered as an explanation of the development of obesity through loss of intake control early in life. Insulin is intimately involved in both long- and short-term intake control and the actions of both insulin and leptin are modified by malnutrition. Programmed development of obesity and adipogenic diabetes in rats has been attributed to a permanent dysregulation of the adipoinsular feedback system, again amplified by a hypercaloric diet, leading to hyperleptinemia, leptin resistance, hyperinsulinemia, and compensatory leptin production by pancreatic \( \beta \) cells [33]. The offspring of undernourished mothers (30% of the ad libitum intake of the control mothers), cross-fostered during lactation to the control mothers, had lower birth weights than the offspring of control mothers [34]. After weaning, they exhibited higher food intake, systolic blood pressure, and fasting plasma insulin and leptin concentrations than control pups. These effects were amplified by a hypercaloric diet (30 vs. 5% fat), prompting the authors to conclude that hyperphagia is programmed in fetal development and exacerbated by environmental factors.

Epigenetic effects of nutrients and other dietary factors (e.g. antioxidants) during embryonic development, not gene mutations, have recently provided a plausible link between genetic makeup and susceptibility to development of chronic diseases [35]. DNA methylation is a major modifier of the genome,
repressing transcription and thus a ‘gene silencing’ mechanism. Early in development, the genes are not methylated, but this process is thought to occur after implantation of the zygote. Methylation occurs through the action of the DNA methyltransferase, a process in which many vitamins participate. Therefore, certain dietary supplements given during pregnancy and early postnatal life may have an unintended silencing or deleterious effect on gene expression [36] as shown by the effect of feeding a diet high in vitamins involved in methyl group metabolism on the expression of coat color in the viable yellow Agouti mouse (Avy). The expression of the Agouti gene is characterized by a yellow coat color, obese, diabetic and cancer-prone phenotype. A 3- to 5-fold higher intake of methyl donors and methylation cofactors in the form of choline, betaine, B12 and folate during pregnancy led to a shift towards offspring with the brown coat color phenotype, indicating an epigenetic regulation of the Avy gene through methylation [36]. The resulting phenotype is characterized by a brown coat color, lean body weight, and normoinsulinemia [37].

The development of the gene expression of gut hormones involved in the regulation of food intake is at present unknown, as is the influence of the composition of food consumed in early life, but this requires exploration. The ability to potentially modify different populations of enteroendocrine cells may become an important therapeutic strategy for treating and/or preventing excessive food intake and obesity [38].

Preliminary data support the importance of epigenetic events in the development of intake control mechanisms [39, 40]. Increasing the vitamin content of the diet fed to Wistar rats, only during pregnancy and after implementation of the zygote, predisposes the offspring to impairment of intake control, altered gut hormone response, insulin resistance and obesity. Altered phenotypic expression due to epigenetic changes appears to be a likely explanation.

**Conclusion**

The advances in understanding the physiology of intake control mechanisms has not led to a food solution for the obesity epidemic. However, they have provided incentive for testing new hypotheses of food- and diet-based strategies and the interaction between food components and physiological responses. Continued research at the level of physiologic and molecular mechanisms shows promise to contribute to a food-based solution to intake control.

**References**


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Discussion

**Dr. Butte:** After the digestion of human milk is there evidence of guanosine monophosphate (GMP)? My second question is, if I followed you correctly in the studies by Waterland and Jirtle [1] increased manipulation lead to leaner animals, but in your study the increased vitamin intake lead to obesity [2]. Could you clarify that?

**Dr. Anderson:** I can't give the reason for the contrasting effect. The Agouti mouse and Wistar rat are different genetically. However, we expected that the increase in vitamin intake would be protective for the offspring in the development of insulin resistance and perhaps enhancing appetite regulation. But we got quite the opposite. Scientists in Nestlé research have done some preliminary studies on the release of GMP during digestion in infants.

**Dr. Butte:** I was just wondering when you were talking about cow's milk. Is there any evidence regarding the release after human milk digestion?

**Dr. Anderson:** There was some discussion of that at the whey protein conference in Chicago in September. GMP appears but the duration, which is what I am uncertain about and whether it has functional significance, was not looked at.

**Dr. Dewey:** In terms of the development of appropriate appetite regulation and control of food intake, is there evidence that overfeeding, i.e. from animal studies, has a negative effect on control of food intake later in life?

**Dr. Anderson:** There are some data that support the notion that overfeeding has health consequences [3], but the effect on food intake control has not been examined.

**Dr. Desjeux:** You mentioned that during fetal life the nutrient could alter genetic programming and it could be an epigenetic phenomenon. We also know that there are direct interactions between nutrients from amino acids to glucose and fatty acids, and direct interactions with genes. Do you know if these interactions could be permanent or could have long-term effects?

**Dr. Anderson:** I think there is very little mechanistic exploration that would explain what is happening to the phenotypic expression. What I neglected to mention is that we have given these mother rats a complete vitamin mix but not at the high amount that Waterland and others have done in order to get the methyl addition to the DNA. From our own studies we don't know which of the vitamin groupings might be

generating the effect. Other mechanisms need to be explored, as you suggested, but currently DNA methylation and histone modification are the favored mechanisms [4].

Dr. Desjeux: Did you purposely not speak on energy density as a regulatory mechanism?

Dr. Anderson: No, I am quite familiar with the volumetric idea and energy density as a factor determining food intake. However, there has been little exploration of physiological mechanisms. Because I am in the center of the glycemic index universe at the University of Toronto, I would like to point out that a high energy-dense, rapidly digestible, high glycemic index food is much more effective in shutting down short-term food intake than is a low glycemic index food [5].

Dr. Pencharz: As I listen to your talk it sounds to me like studying rats is studying rats, and we around this table are mostly interested in people, particularly children, and as you mentioned in fact children behave differently to adults. Thinking for the future, should the focus be on studies in humans or might some other animal model help us understand the mechanisms, or are we stuck with the difficulty of human studies?

Dr. Anderson: I believe that to explore mechanisms you need animal models. For example, with our studies on the effect of high vitamin intakes in the rat and the increase in insulin resistance, surely that provides a motivation to explore whether or not this applies to the human population. But otherwise you would have no justification for entering into a human study.

Dr. Fan Yang: You talked about fetal programming. In our clinic we have found that some babies born with intrauterine growth retardation do not show catch-up growth in later life. Is there any evidence that in utero influences have some effect on the long-term and short-term food intake regulation by the baby which may contribute to the baby losing catch-up growth in later life?

Dr. Anderson: It is assumed that there is a distortion in food intake regulation, but I am unaware of any evidence for this. I think that our own studies provide some justification for trying to understand whether the satiety hormone responses are different in obese vs. normal children and whether or not there is a developmental aspect.

Dr. Yi-hung Choi: Can you comment on the role of other food components including appetizers? Some vitamin or mineral components can have an influence on the food intake of children. Can you also comment on the very early feeding behavior of the caregivers in relation to the food preferences of young infants from a behavioral aspect?

Dr. Anderson: I am certainly no expert on the subject of the impact of caregivers; Dr. Dewey and others could probably answer that question much better than I. The question of whether caregivers giving extra calories influences long-term food intake and the regulatory system is a good one and needs to be explored. Your other question addressed vitamins and minerals; we gave vitamins but one of the reasons for starting to look at milk protein and the biologically active peptides, at least here in North America, is that there have been published associations between dairy consumption and healthier body weight. One of the popular hypotheses relates to calcium and vitamin D metabolism in adipose tissue. Perhaps increased calcium intake is the factor, but it is certainly not the only answer, because the studies that have been conducted suggest that the dairy product itself is more beneficial than simply calcium. We have shown that whey protein reduces food intake more than soy or egg protein. So I think milk proteins and their bioactive peptides are important factors [6]. However, there are minerals that affect food intake regulation, and zinc is a classic example, but that usually is a deficiency that causes anorexia.

Dr. Ziegler: The obesity epidemic seems to be worldwide and concerns us all, and seems to have occurred in parallel with an increase in the use of non-caloric or
low-caloric foods and drinks. Would you care to comment on the effect of non-caloric foods on the regulatory systems?

Dr. Anderson: In our own studies, if you sum up the calories in the preload with what is eaten at the meal, you very often get a net gain in calories over and above what you would get if the preload was a high intensity sweetened beverage. Not only that, we often see that just a sweet taste from a high intensity sweetener tends to suppress food intake at a meal a little more than just the water preload [7]. If you go around the world, there are many dietary patterns that lead to obesity and are associated with economic advancement. So I don't think it is a factor. Generally, calorie-free sweetened beverages lead to less caloric intake than those containing calories [8].

References
