
Special Publication



Appetite and Food Intake Regulation

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Introduction

Considering the importance of food intake to survival, it would seem unlikely that a regulatory system has not evolved to control food intake. Such a regulatory system would operate to ensure that food intake is sufficient to not only to prevent starvation, but to provide adequate energy to support tissue growth and repair as well as sustain reproductive capability. Ongoing research has identified several potential physiological mechanisms that are causally related to food intake and may form the basis of a regulatory appetite system. For example, it has been demonstrated that food intake can be influenced by a number of physiological factors including stomach distention, gut and neuro-hormones and the presence of metabolizable fuels in the blood. In addition, environmental factors such as the presence of palatable food or a habitual meal time have been shown to impact eating behavior. Nonetheless, current understanding of exactly how these physiological and environmental factors interact to influence eating behavior is rudimentary and many questions remain to be answered.

This review aims to critically examine the literature relating to appetite research. It will follow an orderly progression beginning with a discussion of the various internal (physiological) and external (environmental) mechanisms that have been implicated in the appetite regulation, progressing to currently available methods used for measuring appetite, and concluding with an assessment of the current state of appetite research.

Appetite Terminology

Appetite is a general term that encompasses three separate components: hunger, satiation and satiety. *Hunger* describes the sensations that serve to initiate food intake. These sensations may be physiological (stomach rumbling) or psychological (eating in response to stress). Following meal initiation and as eating proceeds, hunger begins to subside while *satiation*, the feelings of fullness and sensations of satisfaction, becomes increasingly dominant. Eventually the feelings of satiation override those of hunger and contribute

to the cessation of eating and the beginning a period of abstinence from eating or an “inter-meal” period. The sensations that dominate during the inter-meal period and, to a large extent, determine its duration, are collectively referred to as *satiety*. Each of these components of appetite—hunger, satiation, and satiety—are multidimensional and are believed to be influenced by metabolic, sensory, and cognitive factors.

Internal (Physiological) Regulation of Appetite

Located in the middle of the base of the brain, the hypothalamus has long been considered the “hub” of the putative physiological appetite regulation system. Early research demonstrated that lesioning distinct regions of the hypothalamus could impact feeding behavior and body weight regulation, thereby supporting its fundamental role in the regulation of appetite. For example, bilateral lesions to the ventromedial hypothalamus (VMH) in rats led to hyperphagia and obesity (Hetherington & Ranson 1940, Keese & Hirvonen 1997). Conversely, bilateral lesions to the lateral hypothalamus (LH) resulted in aphagia and weight loss (Anand & Brobeck 1951). These observations led to the conclusion that the VMH was the brain’s satiety center while the LH was the hunger center.

More recent research has indicated that these hypotheses are simplistic and unwarranted (Orr and Davy 2005). The intervention itself (i.e., lesioning) is crude and may damage other areas of the brain pertinent to eating behavior. Moreover, these lesions do not produce permanent effects. VMH lesioned animals eventually reach a stable body weight, indicating they can develop satiety, albeit at a higher level. Conversely, LH lesioned animals eventually begin eating and also maintain a stable body weight, although at a lower level (Keese and Boyle 1973). Additionally, accumulating evidence indicates that there are a number of other regions in the brain as well as a variety of neuropeptides that

are directly or indirectly involved in the regulation of appetite.

Neuropeptides Involved in Appetite Regulation

To date, several neuropeptides believed to be causally related to eating behavior have been identified. The most well-known of these include neuropeptide Y (NPY), and agouti related protein (AgRP) which are considered orexigenic or appetite stimulating, and proopiomelanocortin (POMC) and cocaine-amphetamine related transcriptase (CART), which are considered anorexigenic or appetite inhibiting.

Orexigenic neuropeptides: During a period of fasting, the hypothalamus responds by increasing the expression of NPY and AgRP (Yoshihara et al. 1996). NPY is currently considered the most the most potent stimulator of food intake. Research indicates that when exogenous NPY is administered to rats, food intake increases markedly (Stanley et al. 1986; Morley et al. 1987). Additional evidence supporting a causal link between NPY and eating is provided by data indicating a rise in NPY release that precedes spontaneous meal initiation (Kalra et al. 1991).

AgRP is another potent stimulator of food intake and exerts its effects by antagonism of the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors, which are the site of action for the anorexigenic breakdown products of POMC. Evidence for a role of AgRP in energy balance is provided by studies that show an increased food intake following administration to rats (Tang-Christensen et al. 2004). Further evidence comes from observations that mice that have been genetically manipulated to over express AgRP develop obesity (Shutter et al. 1997). Conversely, a polymorphism in the AgRP gene is associated with a lower body weight and lower adiposity in humans (Marks et al. 2004).

It is interesting to note, however, that mice that lack the ability to produce NPY or AgRP eat normally and maintain a “normal” body weight (Qian et al. 2002). In contrast, a polymorphism of one receptor in the satiety mechanism (such as the MC4R receptor) leads to over-eating and obesity. These observations suggest that other, as yet

identified, signaling pathways exist that are capable of regulating appetite and energy balance.

Anorexigenic Neurons: Eating suppresses the release of NPY/AgRP and increases the secretion of POMC and CART (Swart et al. 2002), which have been shown to inhibit appetite and food intake. POMC exerts its anorexigenic effects by binding to MC4R and possibly MC3R receptors within the hypothalamus, which lead to the suppression of appetite. In rodent models, the lack of the MC4R leads to over-eating and obesity (Fan et al. 1997). In addition, a polymorphism of the MC4R receptor in humans is associated with polygenic late-onset obesity (Argyropoulos et al. 2002).

CART is expressed in the hypothalamus (Kristensen et al. 1998) and promotes appetite suppressing effects similar to POMC, although a CART receptor has yet to be characterized (Orr and Davy 2005). Studies show that food-deprived animals show pronounced reduction in CART mRNA within the ARC (Kristensen et al. 1998), while injection of CART peptide fragments increases food intake in rats (Lambert et al. 1998). These data suggest that CART is involved in the control of energy homeostasis.

Peripheral Influences on Appetite

In addition to the central neuropeptides, there are a variety of peripheral (i.e., peripheral to the central nervous system) influences on appetite. Some of the more common peripheral regulators of appetite are presented in Table 1 and described in the following paragraphs.

Peripheral Peptides:

Peptides released into the periphery relay information to the hypothalamus relating to energy reserves or recent energy intake. Peripheral peptides can influence the release of appetite related neuropeptides (NPY, AgRP, POMC and CART) through two routes: *directly* through interaction with the relevant neurons or *indirectly* through the interaction

with the vagus nerve (Reidelberger et al. 2004).

Table 1: Peripheral Peptides and Metabolites Involved in Appetite

	Site of Secretion	Impact on Appetite
Peptides		
Peptide YY (PYY)	Ileum	Reduce food intake
Glucagon-like-peptide 1 (GLP-1)	Ileum	Reduce food intake
Insulin	Pancreas	Reduce food intake
Cholecystokinin (CCK)	Duodenum	Reduce food intake
Ghrelin	Stomach	Increase food intake
Leptin	Adipocytes	Reduce food intake
Metabolites		
Glucose	n/a	↑ glucose reduces food intake; ↓ glucose increases food intake

Ghrelin: Ghrelin is a novel 28 amino acid peptide that is predominantly secreted by endocrine cells in the stomach, with smaller amounts secreted in the hypothalamus, and acts to stimulate food intake (Kojima et al. 1999). Ghrelin's role in appetite regulation was brought to the attention of obesity researchers by observations that the administration of the peptide to freely-feeding rats stimulated food intake (Wren et al. 2000). It has also been noted that the expression of ghrelin in rats is increased during periods of fasting while blood levels are suppressed by feeding or infusion of nutrients (Tschop et al. 2000).

Subsequent research has demonstrated that ghrelin is also involved in human feeding behavior. For example, Wren et al. (2001) showed that intravenous administration of ghrelin produces a robust increase in reported hunger and food intake. Additional support for a role of ghrelin in meal initiation is provided by data indicating a pre-prandial rise and post-prandial fall in circulating ghrelin concentration (Cummings et al. 2001; Cummings et al. 2004). It should be noted, however, that at least one other researcher has failed to find a relationship between ghrelin levels and spontaneous meal requests (Callahan et al. 2004). In addition, patients with Prader-Willi syndrome, an inherited condition marked by hyperphagia and obesity, exhibit extremely high concentrations of ghrelin (Haqq et al. 2003), which suggests the possibility of ghrelin resistance. Further research is needed to clarify the physiological specific mechanisms by which ghrelin influences appetite.

Cholecystokinin (CCK): It has been 30 years since it was first reported that rats consumed less food following exogenous administration of CCK (Gibbs et al. 1973). Several subsequent studies have demonstrated a similar effect on human eating behavior (Kissileff et al. 1981; Pi-Sunyer et al. 1982; Muurahainen et al. 1988; Lieverse et al. 1993; Ballinger et al. 1995; Burton-Freeman and Schneeman 2002). CCK is secreted duodenal mucosal cells in response to the presence of macronutrients, particularly fat, in the small intestine (Liddle et al. 1985) and is believed to promote satiety by inhibiting gastric emptying (Moran and McHugh 1982). This belief is supported by observations that the rate of gastric emptying is increased following administration of CCK antagonists (Moran et al. 2001).

While exogenous administration of CCK has a robust effect on appetite suppression, the effects of endogenous CCK are less clear. French et al. (1993) reported a significant negative correlation between plasma CCK concentration and hunger following the provision of a meal in nine healthy adults (French et al. 1993). However, there was substantial inter-individual variation. Moreover, the statistical relationship was likely biased by a couple of outliers, as most of the subjects did not exhibit the predicted inverse relationship between plasma CCK and hunger ratings. A more recent study suggests that there may be a differential gender effect of CCK on appetite suppression. Burton-Freeman and colleagues (2004) found that women had higher plasma CCK concentrations and experienced greater satiety after consumption of various oils compared to men.

Peptide YY (PYY): Synthesized in the distal portion of the gastrointestinal tract as well as the central and peripheral nervous systems, PPT appears to impact appetite by acting directly on the ARC to inhibit the release of NPY while stimulating α -MSH (a breakdown product of POMC) (Batterham et al. 2002; Cowley et al. 2003). There are two primary endogenous forms of PYY: PYY_{1-36}} and PYY

³⁻³⁶. Both are biologically active, but only PPY ³⁻³⁶ demonstrates a high affinity for NPY/AgRP receptors. The ratio of circulating PPY ¹⁻³⁶ to PPY ³⁻³⁶ varies depending on feeding status with higher levels of PYY ¹⁻³⁶ observed during fasting and increasing concentrations of PYY ³⁻³⁶ postprandially.

Research has shown that PYY₃₋₃₆ administered peripherally causes a marked inhibition of food intake in mice, rats and both obese and lean humans (Batterham et al. 2002; Chelikani et al. 2005). For example, Batterham et al. (2002) reported that PYY₃₋₃₆ infusion into humans, at typical postprandial concentrations, reduced food intake by 30 percent. Administration of PPY ³⁻³⁶ also reduces fasting concentrations of ghrelin in both obese and lean individuals and attenuates the normal postprandial rise in ghrelin in lean subjects (Batterham et al. 2003). These findings have raised hopes that PYY ³⁻³⁶ may prove to be an important weapon in the fight against obesity, although a recent report by Tschop et al. (2004) has questioned the efficacy of PYY ³⁻³⁶ as an aid for weight loss.

Glucagon-Like-Peptide-1: GLP-1 is secreted in the ileum in response to the appearance of nutrients, especially fat in the small intestine (MacIntosh et al. 1999). GLP-1 is thought to form part of the “ileal brake” mechanism that adjusts gut transit to ensure a steady and digestible flow of nutrients from the stomach to the intestines. It is through this mechanism that GLP-1 is thought to influence satiety (Zander et al. 2002).

A number of studies have shown that intravenously infused GLP-1 reduces subjective appetite scores as well as subsequent food intake (Flint et al. 1998; Gutzwiller et al. 1999; Flint et al. 2000b; Flint et al. 2001). In these studies, GLP-1 reduced food intake by approximately 12 percent, a figure that was supported by a recent meta-analysis of 11 GLP-1 studies (Verdich et al. 2001a). Unlike some of the other peptides studied, GLP-1 has been shown to reduce food intake at physiological levels; however, it does function in a dose dependent manner; thus it is more effective at slightly supra-physiological levels (Verdich et al. 2001b).

Leptin: The successful cloning of the mouse obese (ob) gene and its human analogue in 1994 led to the discovery of the hormone leptin (Zhang et al. 19994). Leptin is synthesized predominantly in the adipose tissue and has a number of diverse roles in the body, one of which is the signaling of information regarding body fat stores to the hypothalamus (Considine et al. 1996). Not surprisingly, plasma leptin concentrations are highly correlated with peripheral and subcutaneous body fat stores (Hube et al. 1996; Ruhl and Everhart 2001). Exogenous administration of leptin to genetically obese (leptin-deficient) rodents decreases food intake and reduces body weight and body fat. Conversely, obese humans generally have elevated levels of circulating leptin and administration of leptin has produced inconsistent results with respect to weight loss. This finding has led researchers to hypothesize that it is leptin resistance rather than leptin deficiency that plays a role in human obesity (Orr and Davy 2005).

Leptin crosses the blood-brain barrier via a saturable transport receptor and influences food intake by inhibiting NPY/AgRP release and stimulating POMC in the arcuate nucleus of the hypothalamus (Cowley et al. 2003). Research suggests that leptin functions more as long-term regulator of appetite and, consequently energy balance. Chin-Chance et al. (2000) showed that energy deficits of greater than 24 hours led to decreases in leptin concentration that, in turn, reduced the inhibition of neuropeptides that promote eating. Conversely, an energy surplus lasting longer than 24 hours resulted in increased levels of circulating leptin (Chin-Chance et al. 2000) which stimulated POMC and reduced food intake. In addition, research suggests that when food intake is consummate with the body's preferred body-weight, or set-point (assuming this exists), leptin does not appear to be related to appetitive sensations. On the other hand, when energy balance is distorted, posing a threat to the body's preferred weight, leptin levels then become correlated with appetite ratings and food intake (Keim et al. 1998).

Insulin: In addition to its well-known role in glucose metabolism, insulin has been hypothesized to play a role in appetite regulation. This hypothesis is based on the following physiological functions of insulin: (1) it is secreted in proportion to body fat; (2) it has access to appropriate areas of the nervous system; and (3) under certain conditions, it can influence food intake and body weight in predictable ways, i.e., elevated insulin levels in the hypothalamus inhibit food intake and reduced levels stimulate eating behavior (Woods and Seeley 2000).

Nonetheless, despite insulin's documented appetitive roles, the evidence relating insulin to eating behavior is not particularly compelling. In a euglycemic clamp study, (a technique where plasma glucose levels are kept constant through the constant infusion of a glucose solution into a peripheral vein), Rodin et al. (1985) showed that insulin concentrations (that were independent of changes in blood glucose) actually increased hunger ratings. Other studies suggest that under euglycemic or hyperglycemic conditions, insulin has no effect on appetite or food intake (Woo et al. 1984; Gielkens et al. 1998; Lavin et al. 1998). It is likely that insulin's relation to appetite is confounded by its interaction with many other metabolic processes.

Peripheral Metabolites

The primary peripheral metabolite believed to influence appetite is glucose. The potential link between blood glucose levels and food intake has been debated since the early 1900s (Carlson 1916) and, in 1953, was formally presented as the *glucostatic theory* of eating (Mayer 1953). In a paper published in the *New England Journal of Medicine*, Mayer (1953) postulated the existence of glucosensitive detectors in the brain that monitor blood glucose utilization. When these detectors sensed that the arteriovenous difference in blood glucose was zero, (an indication that glucose is not entering cells), hunger was stimulated and eating was initiated. Thus, hunger and food intake were believed to be the response to blood glucose depletion. Conversely, when the arteriovenous difference in blood glucose was positive, this indicated that glucose was available for utilization by the cells and so hunger would be decreased and eating would cease.

Early research appeared to support Mayer's glucostatic theory (Grossman 1986; Campfield and Smith 1990). Administration of insulin or glucose antagonists produced a predictable reduction in blood glucose levels, increased appetite, and induced eating (Grossman 1986). However, flaws in these studies and their interpretations were subsequently articulated and the theory has since fallen from favor. More specifically, it was noted that many of the supporting studies used supra-physiological doses of insulin and reduced blood glucose concentrations to levels not normally experienced in daily living (Van Italle 1990). It is also doubtful whether an efficient appetite system would wait until glucose levels dipped to dangerously low levels before initiating a meal. In addition to these criticisms, euglycemic clamp studies demonstrate that blood glucose does not correlate with subjective hunger ratings (Chapman et al. 1998).

Interaction of Peripheral Peptides

For ease of explanation and understanding, the peptides known to impact appetite were discussed independently. However, it is important to understand that no single peptide or metabolite acts in isolation; rather the action of several of these peptides can be influenced by the concentrations of other peptides as they collectively influence appetite. For example, the infusion of leptin acts synergistically with CCK to reduce food intake (Barrachina et al. 1997; Wang et al. 2000). This suggests that when leptin levels are elevated, due to prolonged overfeeding, CCK's action is increased to reduce food intake. Elevated leptin levels also stimulate the secretion of GLP-1 from intestinal cells (Anini and Brubaker 2003) and collectively they act to reduce appetite and food intake. In line with its potential role as a long-term regulator of appetite, insulin interacts with several gut peptides to augment satiety. For example, insulin release suppresses ghrelin secretion (Saad et al. 2002) and increases sensitivity to CCK (Riedy et al. 1995). These examples illustrate the complexity of the physiological regulation of appetite and highlight the fact that further study of eating behavior will

requires an integration of knowledge from multiple processes.

External (Non-Physiological) Influences on Appetite

While the evidence supporting the internal (physiological) regulation of appetite is compelling, it is important to also recognize the large body of literature indicating that many of the physiological mechanisms believed to be involved in appetite regulation are trainable and, thus, may be influenced by external factors. For example, research has shown that when animals are fed at the same time each day, they learn to synthesize and secrete hormones and neurotransmitters that are putative controllers of food intake such as NPY (Yoshihara et al. 1996). Anecdotal and scientific research also suggests that human eating behavior is readily influenced by external factors such as environmental cues and macronutrient influences.

Environmental Factors Influencing Appetite

A number of environmental factors have been shown to influence human eating behavior. For instance, meals are frequently consumed at certain times during the day simply because it is “meal time” (i.e., the company lunch-hour or habitual family dinner time with little regard to physiological stimuli) (Woods and Strubbe 1994). Similarly, the sight and/or smell of palatable food can be a strong stimulant for eating, even when an individual is “full” and there is no obvious physiological need for additional food (Cornell et al. 1989; Marcelino et al. 2001).

Environmental factors can also override the feelings of satiation. The sensory rewards provided by access to palatable foods often present sufficient stimulus to continue eating even when physiological needs are theoretically met. For example, while rats appear to maintain a stable body-weight when fed standard rat chow, the introduction of a cafeteria-style diet promotes overeating and consequently obesity (Pedrazzi et al. 1998). Similarly, studies using human subjects have reported that the palatability of foods being eaten can promote consumption of a larger meal size (De Graaf et al. 1999; Salbe et al. 2004).

Increasing the variety of foods contained in a meal can also increase food intake, a phenomenon known as “sensory-specific satiety.” According to the sensory-specific satiety theory, as a food is consumed, its palatability decreases while the palatability of other foods remains relatively unchanged (Rolls et al. 1981a). Thus the greater the variety of foods presented, the more likely food intake is to be increased. This theory is supported empirically by research indicating that humans eat more when a variety of sandwiches are offered rather than the same sandwiches in successive courses (Rolls et al. 1981b).

Finally, the size of the presented meal can also strongly influence the amount eaten. For example, Levitsky and Youn (2004) surreptitiously manipulated the portion sizes of meals served buffet style to subjects over a period of several days. On the days when larger portions were served, significantly greater amounts of food were consumed. Moreover, each of the four foods that comprised the meal (i.e., soup, pasta, breadsticks, and ice cream) increased significantly in proportion to the portion size served. A number of other studies, well-controlled, laboratory-based studies have shown that the provision of larger food portions leads to significant increases in energy intake. This effect has been demonstrated for snacks as well as a variety of single meals and shown to persist over a 2-day period (Rolls et al. 2002; Diliberti et al. 2004; Rolls et al. 2004a; Rolls et al. 2004b). Moreover, despite increases in intake, individuals presented with large portions generally do not report or respond to increased levels of fullness, suggesting that hunger and satiety signals are ignored or overridden (Ello-Martin et al. 2005).

In addition to sensory aspects of the eating environment, social factors have been shown to influence eating behavior. For example, research suggests that people generally eat more when they are with a group of people compared with eating alone and the amount eaten tends to increase in direct proportion to

the number of people present (de Castro 1988). The physical surroundings during the meal may also influence food intake. Several studies have shown that the palatability ratings of identical meals increases when the meal is eaten in pleasant surroundings (Stroebele and De Castro 2004). Theoretically, an increase in palatability ratings would translate into an increase in food intake.

Macronutrient Influences on Appetite

A growing body of evidence, derived from both epidemiological and intervention studies, suggests that macronutrients exert differential effects on appetite. In general, these studies indicate that fat is the least satiating of the macronutrients and protein the most satiating (de Castro 1987; de Castro and Elmore 1988) while carbohydrate lies somewhere in the middle. For example, in a study based on 16 diet records collected over one year, fat was positively correlated with total energy intake ($r=0.18$), whereas protein intake was negatively correlated (-0.45). Interestingly, in this study, carbohydrate intake showed no correlation with energy intake (Bingham et al. 1994).

Data obtained from laboratory studies generally confirm the above findings. Hill and Blundell (1989) reported that a high protein meal produced a greater sensation of fullness and a decreased desire to eat, relative to a high carbohydrate meal. A similar study by the same group of authors reported that lean individuals reduced food intake in response to a previous high protein meal (Porrini et al. 1997). A final study by this group of researchers fed a high-protein or a high-carbohydrate lunch to 20 normal weight women and measured energy intake at the subsequent evening meal (Barkeling et al. 1990). Energy intake at the evening meal was reduced significantly more following consumption of the high protein lunch. However, it must be noted that the levels of protein used in the test meals were considerably higher than most people would “normally” consume, ranging from 31 to 54 percent of total daily energy intake. Moreover, the palatability of chronically consuming such large amounts of protein remains to be demonstrated.

Dietary fat has also been shown to influence food intake, but in an opposite manner to that of protein. Research consistently shows that when

animals and humans are allowed to eat ad libitum on high-fat diets more energy is ingested than when fed on lower fat diets (Duncan et al. 1983; Lissner et al. 1987; Tremblay et al. 1991; Thomas et al. 1992). This phenomenon appears to hold true for single eating occasions as well as over a period of several weeks (Lissner et al. 1987; Prewit et al. 1991), indicating that there is generally a lack of compensation for the lower energy density of a low-fat diet. It is hypothesized that the increased fiber content and the greater volume of food consumed on a low-fat diet contributes to greater satiation and consequently fewer calories consumed.

Interestingly, the effect of carbohydrate ingestion on subsequent energy intake remains somewhat controversial. While some research has demonstrated a suppressing effect of carbohydrate intake on subsequent energy intake (Rolls et al. 1994), the response is not robust. Moreover, a number of studies have found no suppression of subsequent energy intake (van Stratum et al. 1978; Rolls et al. 1991). When carbohydrate meals are matched on energy density to high-fat meals, the two meals have comparable effects on appetite. Thus, the energy density property of these two macronutrients may be more important than their chemical structure.

While the above studies appear to demonstrate a hierarchy of the satiating efficiency of macronutrients (protein>carbohydrate>fat), the satiating effects of a given food should not be assumed to be due solely to its predominant macronutrient or even its energy density. Several other constituents and/or characteristics of food have been shown to impact satiety including fiber and water content, the structure and temperature of a food as well as various contextual aspects (i.e., whether the food is seen as snack or meal).

A frequently cited study by Holt and colleagues (1995) examined the satiating effects of 38 commonly eaten foods grouped into six different categories (fruits, bakery products, cereals, snack foods, protein-rich foods and carbohydrate-rich foods). Subjects

consumed 240 kcal (1000 kJ) portions of each food item and their feelings of hunger/satiety were assessed every 15 minutes for a total of 120 minutes using an equilateral 7-point rating scale that ranged from “extremely hungry” to “extremely full.” The subjects were then allowed to eat ad libitum from a standard range of foods and drinks. A Satiety Index (SI) score was calculated for each food by dividing the area under the satiety response curve (AUC) for the given food by the group mean satiety AUC for white bread and multiplying by 100. Significant differences in satiety scores were found both within and between food groups.

Boiled potatoes were the most satiating food with a satiety index seven times that of croissants (the lowest scored food), three times that of the control food (i.e., white bread), and significantly higher than any of the other carbohydrate-rich foods.

The highest average food group SI score was produced by fruits and the lowest by the bakery products. Group mean satiety scores were negatively correlated with both the calorie content and the weight of the foods and beverages consumed immediately after the 120 minutes. In other words, greater satiety ratings led to reduced food intake at the subsequent meal.

Measurement of Appetite

As the previous paragraphs have demonstrated, appetite is an abstract and multidimensional construct and as such cannot be measured directly. This has necessitated the reliance on several indirect methods of measurement. Three of the most commonly used assessment methods are: (1) food intake, (2) hunger and satiety questionnaires and (3) physiological biomarkers. Although other methods of appetite assessment have been developed and used on a limited scale, (e.g., salivation and the microstructure of eating including number of chews, rate of eating, etc.), they are not widely accepted as valid indices of appetite and, thus, will not be discussed here.

Food Intake as an Index of Appetite

It is often assumed that food intake and appetite are so inextricably linked that one invariably

serves as a proxy for the other. If this were true, then simply measuring food intake should provide an accurate assessment of appetite, but unfortunately isn’t this simple. In fact, many factors (e.g., stress, boredom, dieting) can act to uncouple the relationship between appetite and food intake and allow for the consumption of food when physically satiated or refraining from eating when hungry. Furthermore, considering the enormous problems with accurately recording food intake outside of the laboratory, the strength of the relationship between food intake and appetite is tenuous at best. Even in the laboratory setting, while food intake may be accurately recorded, the setting is completely artificial which reduces the external validity of the obtained data.

Questionnaires as Indices of Appetite

A variety of questionnaires have been developed to assess appetite. The most common of these is the *visual analogue scale* (VAS). In fact, most of the other appetite rating scales are simply variations of the VAS. The VAS utilizes a standard set of questions that encompass various facets of hunger, satiation, and satiety. Subjects respond to a question by placing a mark on a line, usually of 100 mm or 150 mm in length, that is anchored at each end with opposing statements such as ‘not at all hungry’ and ‘as hungry as I have ever felt.’ An example of a VAS is presented in figure 2.

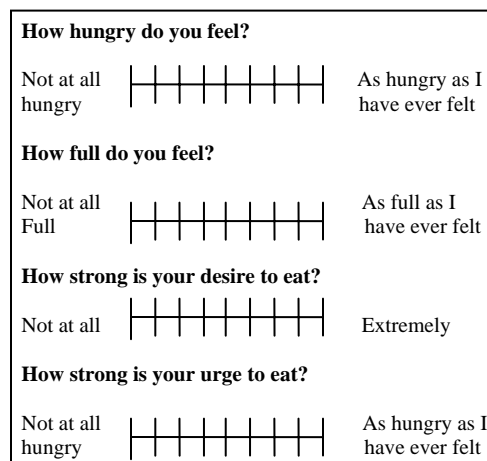
Figure 2: A typical VAS

How hungry do you feel?	
Not at all hungry _____	As hungry as I have ever felt
How full do you feel?	
Not at all Full _____	As full as I have ever felt
How strong is your desire to eat?	
Not at all _____	Extremely
How strong is your urge to eat?	
Not at all hungry _____	As hungry as I have ever felt

While VAS is commonly used as a sole index of satiation in appetite research, its ability to accurately predict subsequent food intake is questionable. In fact, one laboratory-based study found only weak to moderate correlations between VAS scores and subsequent food intake (Flint et al. 2000a). Similarly, a recent meta-analysis of four appetite studies found that while there was a statistically significant relationship between VAS scores and food intake, it was extremely weak accounting at best for only 25 percent of the variation in food intake (Parker et al. 2004). These observations dictate that the results of studies using questionnaires as a solitary index of appetite should be interpreted with caution.

Category scales have also been used to assess subjective appetite ratings (Figure 2). They are used to capture responses to the same questions as VAS. However, rather than one continuous line that is anchored with opposing statements, a category scale will commonly be divided into a number of distinct categories. It should not be assumed that these categories are equally spaced perceptually (e.g., the difference between a 3 and a 4 is not the same as the difference between 8 and 9). Additionally, a hunger rating of 8 should not be taken to mean that it is twice as intense as a hunger rating of 4. Of course, this assumption also applies to VAS.

Figure 3: A Typical Category Scale



A major limitation of appetite questionnaires is that they rely on the subjective experiences of hunger, satiation, and satiety. Thus, they are subject to responder biases and response

distortion. Physiological biomarkers are thought to provide a more objective measure of appetite, although their relationships to hunger, satiation, and satiety are complex and not yet completely understood. Thus, their use in appetite assessment remains somewhat limited.

Physiological Biomarkers of Appetite

As previously described, a number of physiological changes, such as gut peptide concentrations, have been shown to be related food intake and/or appetitive ratings, and, thus, can be used as biomarkers of appetite (Table 1). Interest in the use of biomarkers as indices of appetite or an inclination to eat is based on their presumed lower susceptibility to modification by cognition and environmental factors. This may not be a valid assumption as cognitive or sensory influences may influence potential biomarkers. Well-documented examples include cognitive and sensory influences on salivation, salivary composition, gastric acid secretion, gastric motility, gastrointestinal peptide release, and pancreatic exocrine and endocrine secretions (Melchior et al. 1994).

Table 2: Commonly Used Biomarkers of Appetite

Biomarker	Association with appetite
Cholecystokinin	Satiation
Glucagon-like-peptide 1	Satiety
Ghrelin	Meal initiation
Leptin	Energy stores
Stomach distention	Satiation

For a biomarker to be useful, it must meet a number of criteria. Perhaps most importantly, the measurement of the biomarker must be feasible and measurable without incurring undue stress or require overly invasive procedures. The biomarker must clearly relate to appetite physiology and be sensitive to changes in appetite. Furthermore, measurement of the biomarker must be reproducible under similar conditions (Diplock et al. 1999).

Appetite Regulation and Popular Weight Loss Programs

Several currently popular diet programs/weight loss plans are loosely based on some of the basic tenants of appetite regulation. These programs aim to optimize satiety and/or satiation, thereby reducing energy intake and theoretically promoting weight loss. Examples include the volumetric diet, high protein (low-carbohydrate) diets and diets emphasizing the glycemic index.

“Volumetrics”

The volumetric weight loss plan is based on research that shows that people tend to eat a constant weight of food regardless of the energy density (kcal or kJ per g of food). In other words, it is the “volume” of food as opposed to the calorie content that impacts satiety. Thus, maintaining or increasing the volume of food, while reducing the energy density (by consuming foods high in water and fiber and low in fat content) should result in reduced energy intake.

In the laboratory, the volume of food consumed has been shown to exert a profound effect on energy intake (Prentice and Poppitt 1996; Rolls and Bell 1999; Devitt and Mattes 2004). Participants in these studies tend to eat a similar amount of food regardless of how the energy density of the food has been covertly manipulated, supporting the notion that the volume of food plays a greater role in satiety than the energy density. Nonetheless, caution should be exercised when interpreting the findings from these studies as there are several methodological issues that could bias the results. First, by covertly manipulating the test food the learned cues that people develop, (and that may play a role in dictating eating behavior) are removed, thereby reducing the external validity of the data. Second, limited data cast doubt on the assertion that the weight of food consumed each day is stable (Stubbs et al. 1998) For example, Stubbs et al. (1998) examined the effects of covertly altering energy density of mixed and medium fat diets on ad libitum food intake, subjective hunger, and body weight in normal weight men. The results indicated that food intake of the subjects decreased as energy density of the diet increased. Nonetheless, the reduced intake could not fully compensate for the greater energy content of the

high-energy density diet as subjects still gained significantly more weight on the high- vs. low-energy density diet. The discrepancy among study findings illustrates that additional long-term, free-living studies are required before any definitive recommendations can be made regarding the volumetric diet.

Glycemic index

Almost all carbohydrates, regardless of the form in which they are consumed (e.g., starch, lactose, sucrose) are metabolized to the monosaccharide glucose, which then enters general circulation causing a temporary rise in blood glucose levels. This “glycemic response” is the basis for the increasingly popular measure known as the glycemic index (GI) (Jenkins et al. 1981). The GI is operationally defined as *the incremental area under the blood glucose curve (AUC) after the ingestion of 50 grams of a test food, expressed as a percentage of the AUC of an equal amount of a reference food (generally glucose or white bread)* (Jenkins et al. 1981). A substantial number of foods have now had their GI quantified in a standardized fashion and have been collectively published (Foster-Powell et al. 2002).

The GI as been gaining popularity as potential dietary tool for regulating appetite and managing body weight (GI revolution). More specifically, it has been hypothesized that low GI foods produce greater satiety than high GI foods and, thus, may serve to aid in weight loss (Brand-Miller et al. 2005).

While a number of single-meal test studies have indicated that low GI foods are associated with increased satiety (Holt et al. 1992; van Amelsvoort and Weststrate 1992), delayed onset of hunger (Benini et al. 1995) or decreased ad libitum energy intake (Rigaud et al. 1998; Ludwig et al. 1999) others have shown just the opposite (Chapman et al. *Am J Physiol* 1998, Gielkins HAJ et al. *Metabolism* 1998, Lavin et al. *AJCN* 1998, Holt et al. 1996). For example, Holt et al. (1996) investigated whether postprandial glucose and insulin responses were related to concurrent changes in satiety. Using identical

methodology to that used in the study described previously (Holt et al. 1995), the authors found that there were no significant relationships between satiety, plasma glucose or insulin responses among the 38 test foods. However, a negative correlation was found between insulin responses and ad libitum food intake at 120 minutes, which suggests that test foods producing a *higher insulin response* were associated with less food intake and thus, indirectly, greater satiety. In this particular study, total carbohydrate content appeared to have been a stronger determinant of short-term satiety in conjunction with the food's structural characteristics than with the food's glycemic impact.

There is currently a dearth of long-term studies specifically relating to the effect of GI on body weight. Existing research indicates that the GI (or GL) of the diet has very little impact on weight loss (Table 3).

Due to technical issues with the calculation of GI and difficulties with successfully implementing a low GI diet, the concept of GI may be of little more than academic interest. Moreover, for GI to be useful as a dietary planning tool it must have a predictable effect on the blood glucose area under the curve. For many foods, this is not the case. In fact, the GI of a carbohydrate-rich food can vary significantly depending on the way in which it is processed or prepared, the cooking method used, as well as the variety (i.e., white rice vs. wild rice), origin (i.e., where it was grown), maturation and/or degree of ripeness (Pi-Sunyer 2002). In addition, there is substantial inter-individual (i.e., between subject) variation in glycemic responses to the same food (Foster-Powell et al. 2002). For example, data from the most recent International Tables of Glycemic Indexes (Foster-Powell et al. 2002) indicate that the range of GI values for glucose (chosen as the "reference" carbohydrate for its supposed reliability of measurement) was 85–111 (or a variability of 25 percent!) depending on the population (i.e., type of subjects) studied. Even for foods that require no preparation before ingestion, such as whole milk and ice cream, the GI varied from 11 to 40 and from 36 to 68, respectively.

The concern of reliability is highlighted by a study comparing the GI of four centrally distributed foods (instant potatoes, rice, spaghetti and barley) measured in seven separate laboratories (Wolever et al. 2003). The difference between the highest and lowest measures of the GI of instant potatoes was 33 units. Given that these were apparently identical potato products, it certainly calls into question the reliability of the measure.

Not only does the GI of similar food differ between individuals, they can vary significantly in the same person on different occasions. In fact, the variation within subject can sometimes be greater than the variation between subject. Wolever et al. (1985) showed that for repeated tests of 50 grams of carbohydrate from glucose or bread, the coefficient of variation of AUC was approximately 15 percent in subjects with type 2 diabetes, 23-25 percent in non-diabetic subjects, and 30 percent in subjects with type 1 diabetes.

Due to the technical and practical issues surrounding the GI concept, it is difficult to recommend a low GI diet as one that will predictably curb appetite. While dietary practices may help to moderate food intake, foods are complex systems containing more than one macronutrient in different proportions that may differ in bioaccessibility. Water content may be markedly different altering the volume of the food eaten or energy density. The sensory properties of the foods differ as do postprandial blood glucose dynamics. As each of these have been observed to independently affect appetite it is unlikely that examining any of these variables in isolation will explain much of the variation observed in eating behavior.

High-Protein (Low-Carbohydrate) Diets

As protein is widely regarded to be the most satiating of the macronutrients, it is reasonable to presume that a high-protein diet would be more satiating than a high-carbohydrate diet, thereby reducing energy intake and aiding in weight loss. While logical in theory, this hypothesis has not been supported by

scientific research. Moreover, it should be noted that one of the most popular “high-protein diets,” the Atkins Diet, is actually a high-fat (vs. high-protein), low-carbohydrate diet.

In a recent study, Weigle and colleagues (2005) concluded that a high-protein diet produced greater reduction in hunger ratings and ad libitum energy intake than a low-protein diet. However, it should be noted that this study used a dietary regime that held carbohydrate intake constant while manipulating the fat and protein content to produce a high-protein (30 percent of energy intake) or normal protein (15 percent of energy intake) diet. Consequently, the low-protein diet contained more fat (35 percent of energy intake) and was more energy dense. Therefore, it is not possible to say whether the observed effect was due to the protein content of the diet or the energy density.

From a weight control perspective, it is important to determine whether the hypothetical effects of a high-protein, low-carbohydrate diet on satiety will translate to weight loss. While short-term studies (< six months) have generally supported the efficacy of low-carbohydrate diets for weight control, long-term studies (> six months) generally find that there is no weight loss advantage to these diets (Foster et al. 2003; Stern et al. 2004). For example, Foster et al. (2003) randomly assigned 63 obese men and women to either a low-carbohydrate, high-fat (Atkins) diet or a high-carbohydrate, low-fat (conventional) diet for one year. Mean weight loss was significantly greater on the Atkins diet at three and six months, however the difference was no longer significant at 12 months. In a similar study, Stern et al. (2004) randomly assigned 132 obese individuals to either a low-carbohydrate diet (≤ 30 g/d carbohydrate) or a conventional low-fat diet (<30 percent of total energy intake from fat) for one year. At three and six months, those on the low-carbohydrate diet had lost significantly more weight than those on the low-fat diet; however weight loss in both groups was similar.

In addition to the studies described above, other research has failed to find greater weight loss on a high-protein diet regimen (Noakes et al. 2005; Sargrad et al. 2005). Thus, current research does

not support a weight control advantage from consuming a high-protein, low-carbohydrate diet.

Conclusion

The prevalence of obesity has been increasing rapidly over the past four decades with little end in sight. The pervasiveness of obesity and its comorbidities has contributed to its recent delineation as an “epidemic.” If successful interventions are to be developed to combat this epidemic, it is vital that factors influencing energy intake are identified.

Accumulating evidence supports the presence of a physiologically regulated appetite “system” that maybe amenable to environmental influences. In this system, information relating to energy balance is collected from the periphery and then relayed to several neural sites which ultimately impact sensations of hunger and satiety. If the body is in negative energy balance, appetite promoting neuropeptides are released to induce sensations of hunger and subsequent food intake to correct the imbalance. Conversely, if the body is in positive energy balance, neuropeptides that suppress appetite are secreted thereby increasing satiety and reducing food intake.

Although a variety of physiological (e.g., neuropeptides, peripheral peptides) and environmental (meal size, macronutrient content, sight and smell of food) influences on appetite have been identified, the purpose of the appetite system still needs to be elucidated. Such an explanation is required for practical as well as academic reasons. If appetite is the corrective action which maintains a set body weight, then interventions that aim to reduce food intake by increasing feelings of satiety are likely to fail as the body will up-regulate appetite to negate any weight loss. Alternatively, such intervention strategies may work if the appetite system is not trying to maintain a set body weight (i.e., is trying to promote maximum weight gain).

A number of interventions that reduce appetitive sensations and food intake have

been proposed (e.g., manipulating energy density, altering macronutrient composition). While these interventions appear promising, much of the data is either epidemiological in nature or from single

meal studies and, thus, should be interpreted cautiously. Long-term studies are needed to substantiate the efficacy of these treatments.

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Figure 1: Peripheral Peptides Involved in Regulating Appetite

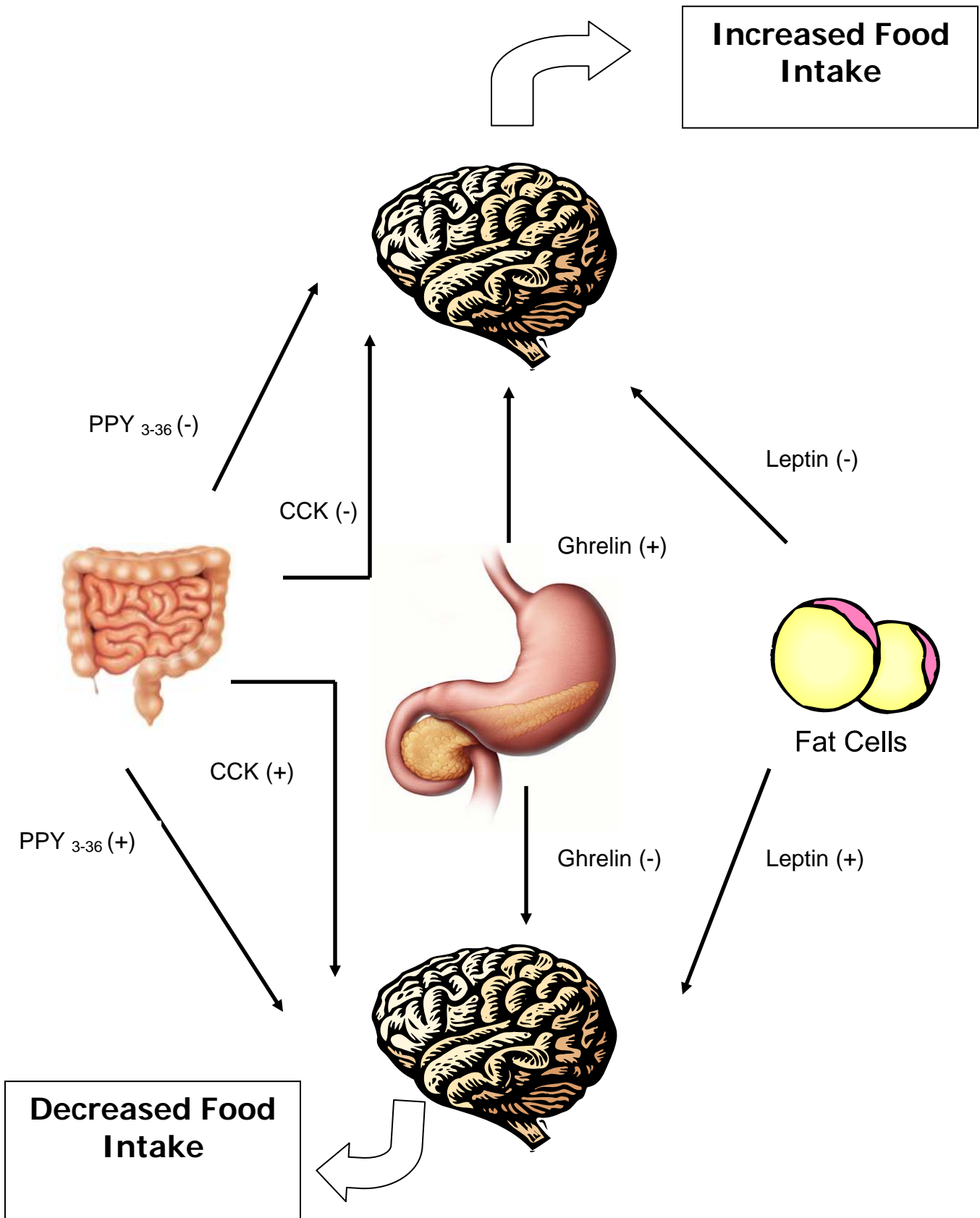


Table 3: Efficacy of Low-GI Diets Compared to High-GI Diets or Low-Fat Diets on Weight Loss

Reference	Duration	Diets	Weight Loss Differences
Isoenergetic			
Jenkins et al. 1985	4 weeks	L-GI vs. LF diets	L-GI > LF
Jenkins et al. 1987a	2 weeks	L-GI vs. H-GI diets	NS
Jenkins et al. 1987b	4 weeks	L-GI vs. H-GI diets	L-GI > H-GI
Santacroce et al. 1990	2 weeks	L-GI vs. H-GI diets	H-GI > L-GI
Brand-Miller et al. 1991	12 weeks	L-GI vs. H-GI diets	NS
Fontvielle et al. 1992	5 weeks	L-GI vs. H-GI foods	NS
Frost et al. 1994	12 weeks	L-GI vs. H-GI foods	NS
Frost et al. 1998	3 weeks	L-GI vs. H-GI foods	NS
Luscombe et al. 1999	4 weeks	L-GI vs. H-GI foods	NS
Jarvi et al. 1999	24 days	L-GI vs. H-GI diets	NS
Tshillas et al. 2000	6 months	L-GI vs. H-GI breakfasts	NS
Giacco et al. 2000	24 weeks	L-GI vs. H-GI foods	NS
Alfenas & Mattes 2004	8 days	L-GI vs. H-GI diets	NS
Energy Restricted			
Wolever et al. 1992	6 weeks	L-GI vs. H-GI foods	NS
Slabber et al. 1994	12 weeks	L-GI vs. H-GI diets	NS
Spieth et al. 2000	4 months	L-GI vs. LF diets	L-GI > LF
Agus et al. 2000	6 days	L-GI vs. H-GI diets	NS
Ebbeling et al. 2003	6 months	L-GI vs. LF diets	NS
Frost et al. 2004	12 weeks	L-GI vs. LF diets	NS
Ad Libitum			
Raben et al. 1997	2 weeks	L-GI (sucrose) H-GI (starch)	H-GI > L-GI
Boche et al. 2000	5 weeks	L-GI vs. H-GI diets	NS
Sloth et al. 2004	10 weeks	L-GI vs. H-GI diets	NS

* *Low-GI (L-GI); High GI (H-GI), Low-Fat (LF)*