Biomarkers of satiation and satiety[1,2]

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ABSTRACT

This review's objective is to give a critical summary of studies that focused on physiologic measures relating to subjectively rated appetite, actual food intake, or both. Biomarkers of satiation and satiety may be used as a tool for assessing the satiating efficiency of foods and for understanding the regulation of food intake and energy balance. We made a distinction between biomarkers of satiation or meal termination and those of meal initiation related to satiety and between markers in the brain [central nervous system (CNS)] and those related to signals from the periphery to the CNS. Various studies showed that physicochemical measures related to stomach distension and blood concentrations of cholecystokinin and glucagon-like peptide 1 are peripheral biomarkers associated with meal termination. CNS biomarkers related to meal termination identified by functional magnetic resonance imaging and positron emission tomography are indicators of neural activity related to sensory-specific satiety. These measures cannot yet serve as a tool for assessing the satiating effect of foods, because they are not yet feasible. CNS biomarkers related to satiety are not yet specific enough to serve as biomarkers, although they can distinguish between extreme hunger and fullness. Three currently available biomarkers for satiety are decreases in blood glucose in the short term (<5 min), which have been shown to be involved in meal initiation; leptin changes during longer-term (>2–4 d) negative energy balance; and ghrelin concentrations, which have been implicated in both short-term and long-term energy balance. The next challenge in this research area is to identify food ingredients that have an effect on biomarkers of satiation, satiety, or both. These ingredients may help consumers to maintain their energy intake at a level consistent with a healthy body weight. *Am J Clin Nutr* 2004;79:946–61.

KEY WORDS Appetite, satiety, satiation, obesity, biomarker

INTRODUCTION

Humans eat in episodes, ie, meals and snacks (1, 2). With meals, people usually eat until they are comfortably full (satiation), after which they do not eat for a certain time (satiety) (3, 4). Immediately after a meal, there is a low drive to eat. This drive builds up again until the moment of the next eating episode. The moment of the next episode is not only dependent on internal factors, but to a large extent is also determined by external (conditioned) environmental factors (cues) (5–7). Many of environmental cues are highly dependent on the time of the day. Humans eat not only to satisfy their appetite but also for many other reasons, eg, sensory hedonics, sensory stimulation, tension reduction, social pressure, and boredom (8, 9). This review focuses on the internal factors that affect appetite.

Appetite is the internal driving force for the search, choice, and ingestion of food. Appetite in humans can be measured in 2 ways. First, it can be measured with the help of subjective ratings. Humans have a capacity for introspection and can rate the strength of their conscious drive or motivation to eat. When used appropriately, subjective ratings have been shown to be reproducible, sensitive to exposures of food components, and predictive of food intake (10–12). However, it should be realized that "appetite" may not always be accessible to introspection (13). In addition, people do not always eat when they are hungry, and they do not always refrain from eating when satiated (14).

Most investigators who use rating scales to assess appetite use the terminology developed by Rogers and Blundell (15) at the end of the 1970s: ie, hunger, desire to eat, prospective consumption, and fullness. These terms relate to slightly different aspects of the motivation to eat. Prospective consumption (or "How much can you eat?") seems to be an easier and more concrete question than a more abstract question about hunger. "Hunger" may refer to the appetite for a meal, whereas "desire to eat" may refer to a milder, pleasant feeling of appetite for a snack. "Fullness" refers to a fullness sensation in the stomach. Because subjects may differ in their response behavior, these scales are preferably used in within-subject studies, where subjects participate in more than one experimental condition.

Second, appetite can be measured by actual food intake; that is, the amount of food eaten within a certain context can be considered as a measure of appetite. The degree to which actual food intake reflects appetite is debatable. There are many factors that may intervene between appetite and actual food intake: cognitive factors, such as dietary restraint, but also external factors, such as availability, hedonic properties of food, and social circumstances. However, when measured under standardized conditions, actual food intake serves as a post hoc indicator of appetite. One important consideration in this respect is that the actual food intake should be observed (ie, directly measured) and not derived from dietary records in which subjects record their own food intake. It is difficult to obtain a precise and valid estimate of energy intake on an individual level from dietary records alone

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TABLE 1
Evaluation of potential biomarkers of satiety according to 6 criteria[1]

Candidate biomarkers	Causal factor in appetite, or indirect measure	Feasibility of measurement	Validity (plausible mechanism)	Sensitivity or specificity (strength of relation with appetite)	Reproducibility (consistency in findings)	Effect of food components
Satiation						
Brain image sensory						
Specific satiety	Indirect	−	+	+	+	−
Stomach fullness	Indirect	+	+	+	+	+/−
CCK	Causal	+	+	+	+	+
GLP-1	Causal	+	+	+	+	+/−
Bombesin	Unknown	+	+	−	−	−
Somatostatin	Unknown	+	−	−	−	−
Satiety						
Brain imaging of satiety	Indirect	−	+	−	+	−
Diet-induced thermogenesis	Indirect	−	+/−	+/−	−	+
Body temperature	Indirect	+	+/−	−	−	−
Absolute glucose	Indirect	+	−	−	−	+
Glucose decreases	Causal	+/−	+	+	+/−	+/−
Insulin	Causal	+	+	−	−	+
Leptin, short-term	Causal	+	+	−	−	−
Leptin, negative energy balance	Causal	+	+	+	+/−	+/−
GIP	Causal	+	+	−	−	−
Ghrelin	Causal	+	+	+	+	+/−
PYY	Causal	+	+	+/−	+/−	+/−
Enterostatin	Causal	+	+	−	−	−

[1] CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; PYY, peptide YY.

(16, 17). Measurements of food intake in experimental artificial circumstances suffer from a lack of external validity in relation to eating in the normal context of eating behavior (9). However, because the measurement of food intake in this context has the purpose of reflecting the internal drive to eat, that seems the appropriate way of measuring appetite.

In the view of Blundell et al (4), the expression of appetite is reflected in the relation between 3 operational levels: *1*) the level of psychological events and behavior, *2*) the peripheral physiology, and *3*) the central nervous system (CNS). The objective of this review is to give a critical summary of published data on the relation between biological or physiologic measures and either subjective ratings of appetite or actual measures of food intake.

The physiologic measures that relate to subjectively rated appetite, actual food intake, or both are defined as biomarkers of satiety and satiation. Markers can be either indicators of appetite, or they can be proven to be causal factors of appetite (18). According to Diplock et al (18), markers should be feasible, valid, reproducible, sensitive, and specific. The requirement of feasibility means that markers must represent relatively immediate outcomes, which can be used to assess effects of interventions within a reasonable time. This is usually not a problem with short-term markers of appetite, ie, within meals or between meals, but it is a problem with markers considered to be involved in the long-term regulation of energy homeostasis. Markers should be measurable in easily accessible material or obtainable by using methods that are both ethical and minimally invasive. The requirement of validity in this context has to do with the notion that the markers must be clearly linked to the physiology of appetite. The sensitivity and specificity in this context reflect the strength of the relation between the marker and the measures of appetite. The requirement of reproducibility reflects the consistency of effects or relations between different studies. In this review, we evaluate the usefulness of the markers according to these criteria (**Table 1**).

Knowledge of and insight into biomarkers of satiation and satiety serve 2 main purposes. First, biomarkers of satiety could be used as a tool or index with which to measure the satiating efficiency of foods. These tools may serve as a basis for type A claims with respect to functional foods, ie, that a certain food or food ingredient enhances satiety, reduces appetite, or does both (18). Second, it helps to understand the physiologic mechanisms behind the regulation of food intake and energy balance in humans. Of course, this process also works the other way around, ie, an understanding of physiology of appetite may yield biomarkers of satiety.

The conceptual framework of Blundell (3) and Halford and Blundell (19) is used as the guiding principle for the organization of this review. Therefore, the main division in this review is between factors that influence meal termination (satiation) and factors that determine meal initiation (satiety). In many reports, the term "hunger" is used, and this can be considered the opposite of "satiety." A lesser feeling of satiety or a higher level of hunger is related to meal initiation. A second division is that between peripheral physiology markers and CNS markers. This review uses those studies that have produced actual data on the relation between physiologic measures and behavioral (ie, intake) or subjective measures or both. Physiologic measures in this review include blood measures, measures derived from imaging techniques, and measures of thermogenesis.

SEARCH METHODS

Reports were identified with the help of the Medline database accessed at http://www.ncbi.nlm.nih.gov/pubmed/. The key words or terms used were *appetite*, *food intake*, *human* in combination with the names of substances [eg, glucose, leptin, cho-

lecystokinin, glucagon-like peptide 1 (GLP-1), peptide YY (PYY), insulin, glucose, leptin, and ghrelin], techniques [ie, *functional magnetic resonance imaging* (fMRI) and *positron emission tomography* (PET scan)], concepts (*sensory-specific satiety*), and other potential biomarkers (eg, *thermogenesis*). The closing date for searches was 15 October 2003. Additional reports were identified from a review of references cited in the reports located by using a Medline search.

PERIPHERAL AND CNS MARKERS INVOLVED IN SATIATION

Studies on meal termination show that the main reason to stop eating at the end of a meal is fullness or absence of hunger, which refers to a sensation of fullness in the stomach (20, 21). Another reported reason is a decline in the pleasantness or reward value of the food being eaten (20, 21). The sensation of fullness is related to peripheral physiologic measures. The sensory reasons to stop eating are primary CNS phenomena. The relative contribution of pleasantness and fullness to meal termination depends on the balance between these 2 factors. Very pleasant-tasting meals may result in a higher food intake and a greater fullness at meal termination.

Meal termination depends on short-term signals such as stomach distension and on gut hormones such as cholecystokinin (CCK) and GLP-1. Sensitivity to these short-term signals is affected by signals that work in the long term, such as leptin, insulin, and ghrelin (22–24). A low leptin concentration (eg, that observed after a few days of energy restriction) may limit the satiating effect of CCK, which leads to a higher food intake during a meal, thereby restoring energy balance. This mechanism explains how long-term signals operate to affect short-term intake. The long-term regulators are most relevant to the pathophysiology of obesity. However, knowledge about the operation of the short-term signals is essential to an understanding of the regulation of energy intake.

BIOMARKERS OF SATIATION IN THE CNS

Before dealing with central biomarkers of satiation, we provide a short explanation of the 2 main techniques that are currently available for measuring human brain responses that relate to appetite.

Introduction to functional neuroimaging techniques

The rapid development of brain imaging techniques during the past decade has led to noninvasive methods of measuring brain function in response to various stimuli. The 2 most important techniques employed in the study of appetite are PET and fMRI. For comparative reviews, see previous publications (25, 26).

In PET, the positron-emitting radioisotope ^{15}O incorporated in water molecules is administered intravenously and distributed to tissues throughout the body. Because it readily crosses the blood-brain barrier, it can be used to measure cerebral blood flow (CBF). At the site of a brain activation, blood flow increases, which leads to greater uptake of the ^{15}O water tracer into brain tissue, which in turn results in an increase in the number of gamma rays detected at that site. Thus, with PET, the local hemodynamic changes accompanying neuronal activity can be measured (27). Because the half-life of ^{15}O is ≈2 min, it is possible in practice to acquire a PET image every 8–10 min. This interval makes PET scans more suitable as a marker of satiety than as a marker of satiation. Subtraction of an experimental image from a baseline image yields an image of the changes in regional CBF (rCBF). The spatial resolution of these images is 5 mm at best.

During an MRI procedure, the subject is placed in a strong magnetic field, which magnetizes the tissues. Then, radiofrequency pulses are applied to excite protons (hydrogen atoms, chosen because they are abundant in biological tissues). On returning to a state of equilibrium, the protons emit radiowaves, which are detected by a receiver coil. The time course of this relaxation process differs among tissues, and that difference is the source of contrast in MRI. In fMRI, the blood oxygen level–dependent (BOLD) signal is used as a measure for neuronal activity. BOLD fMRI makes use of the paramagnetic properties of endogenous deoxygenated hemoglobin as a source of contrast (28–30). Deoxygenated hemoglobin locally distorts the magnetic field and thus affects the relaxation process. At the site of brain activation, increased local blood flow leads to a decreased concentration of deoxygenated hemoglobin, which in turn attenuates the local distortion of the magnetic field and results in a small increase (1–5%) in the fMRI signal. Because the BOLD signal relies on the mismatch between the increase in local blood flow and local oxygen uptake, which varies among subjects and occasions, it cannot be used to quantify rCBF. The spatial resolution of BOLD fMRI can be as high as 1 mm^3, depending on the field strength and other scanner characteristics. However, the BOLD response does not colocalize perfectly with the actual spot of neuronal activation. Temporal resolution in scanning terms can be as high as 64 images/s, but it is ultimately limited by the temporal characteristics of the hemodynamic response, which is the basis of the BOLD signal. The BOLD signal rises 2–3 s after neuronal activation and is back at baseline after ≈10 s (31). The high temporal resolution of fMRI makes it suitable for measuring brain responses that can serve as markers for satiation.

CNS measures related to pleasantness of food and sensory-specific satiety

Numerous studies have shown that the food intake during a meal is positively related to the sensory pleasantness of the food (32). Apart from that, humans eat more from meals with a variety of foods than they eat from meals containing a single food (33). This phenomenon is caused by sensory-specific satiety, which was defined by Rolls et al (34, 35) as a greater decrease in the pleasantness of an eaten food than in the pleasantness of an uneaten food. Sensory-specific satiety can be conceived as an important driver for meal termination and the variety in food choices that humans make from meal to meal and from day to day (33, 36).

Studies on brain biomarkers of satiety conducted by using fMRI or PET scans showed that the (un)pleasantness of taste and olfactory stimuli is represented in the amygdala and the orbitofrontal cortex (37–40). Zald and Pardo (38) found an association between neural activities in the left amygdala and subjective ratings of perceived aversiveness of olfactory stimuli. The role of the left amygdala in aversiveness was confirmed by the response to the taste of a strong quinine solution (39).

In one study focusing on sensory-specific satiety, subjects rated the pleasantness of banana and vanilla odors before and after eating bananas to satiety (41). As could be expected from earlier sensory-specific satiety studies, the subjectively rated

pleasantness of the banana odor decreased more than did the pleasantness of the vanilla odor. Although various other brain areas were involved in the perception of the odors, the orbitofrontal cortex was the only area in which, in all subjects, there was a decrease in neural activity parallel to the decrease in pleasantness (41). A PET study on brain activity changes in subjects who had eaten chocolate beyond satiety showed that the medial orbitofrontal cortex was activated when the chocolate was liked, whereas the lateral orbitofrontal cortex was activated when the consumption of chocolate became aversive (42).

The recent studies that used PET and fMRI techniques to study brain activity clearly showed that the neural correlates of the pleasantness of foods and changes in rated pleasantness of foods during meal consumption can be reliably detected in the brain. Limitations to these techniques are that fMRI and PET scans are not easily carried out or widely available and are relatively expensive. Data from fMRI and PET scans are indirect indicators of neural activity, and therefore they cannot be considered as causal factors in the chain of events leading to satiation. The fMRI and PET scan techniques can be performed only in subjects in the supine position and with the head restricted to prevent movement, and these circumstances for carrying out the measurements are rather artificial. All of the above makes it unlikely that these techniques will be used in the near future to support a claim for the satiety-enhancing capability of functional foods. However, these techniques do represent an exciting contribution to the understanding of the biology of food choice and food intake regulation.

BIOMARKERS OF SATIATION IN THE PERIPHERAL PHYSIOLOGY

Physical measures related to stomach distension

The results of many short-term intake studies show that the weight or volume, rather than the energy content, of foods is one of the most important determinants of meal size (eg (43). For example, when one serves human subjects ad libitum a familiar food (eg, yogurt) with covertly varied fat concentrations, the weight or volume intakes are similar, but the fat and energy intakes are linearly related to the fat concentration (44, 45). These findings indicate that physical measures (biomarkers) that are directly related to the effect of weight or volume of food may also be related to satiation. Stomach distension, fullness, or both seem to be the most obvious candidates for such a measure.

The role of stomach distension in long-term energy homeostasis is less clear. In the short term, a higher energy density linearly increases energy intake, but, in the long term, a high energy density appears more effective in decreasing food intake (46). Gastric capacity may also change over time because of dieting (47).

The role of stomach distension in satiety and food intake is clear from a series of studies of Geliebter et al(47–49) and Geliebter (50). In one of the earliest of these studies, Geliebter showed that stomach capacity, measured by filling a balloon in the stomach, had a correlation of 0.44 ($n = 8$ subjects) with the ad libitum intake from a liquid lunch meal (50). In that study, gastric balloons with a volume of >400 mL reduced food intake. In a later study that included normal and bulimic subjects, the correlation coefficient between gastric capacity and ad libitum liquid meal intake was 0.53 ($n = 18$ subjects; 49).

Other studies providing insight into the role of stomach distension are those with the gut hormones GLP-1 and CCK. GLP-1 and CCK serve as a kind of traffic police assisting with a constant manageable influx of nutrients from the stomach into the gut. GLP-1 and CCK work through effects on pyloric pressure, stomach motility, and stomach muscle relaxation, causing a delay in gastric emptying and a subsequent increase in gastric distension (51). Gastric filling is even a required condition for the satiating effect of CCK (52).

More direct evidence for the role of gastric distension in appetite comes from studies by Melton et al (52) and Cecil et al (53). Melton et al (52) showed in 4 subjects a positive correlation between gastric pressure rise due to balloon inflation and fullness ratings. Cecil et al (53) showed in a study with 9 subjects that covert and overt intragastric infusion of tomato soup suppressed subjectively rated appetite, whereas intraduodenal infusions of soup did not lead to a reduction in subjectively rated appetite. The correlation coefficients between mean appetite ratings and mean gastric content measures were ≈0.99. Regression analyses within subjects showed that gastric content measures could explain ≈50–60% of the variance in the fullness ratings during overt and covert intragastric soup delivery. Rolls and Roe (54) showed that increasing the volume, but not the energy content, of gastrically infused food reduced hunger ratings and food intake in 29 obese and 25 nonobese women.

In summary, there is much indirect and some direct evidence that there is a direct, inverse relation between gastric distension and appetite. A number of methods have become available to measure this "biomarker." For example, the volume required to produce a rise of 5 cm in water pressure (47), gamma-radiation camera measures of radioactive isotopes in the stomach of radioactive isotopes mixed with ingested food (53), paracetamol absorption in the blood of paracetamol mixed with food (51), and MRI (55) are indirect measures of gastric distension. These notions suggest that markers of stomach distension are feasible, valid, reproducible, sensitive, and specific. Moreover, stomach distension is likely to be a causal factor in the chain of events leading to meal termination or satiation. From this perspective, it is clear that measures of gastric distension or fullness may serve as a useful biomarker of satiation. More research may also be focused on more direct physiologic measures of gastric distension, which are the direct biomarkers.

Hormonal or physiologic measures

When food enters the stomach and the gut, numerous hormones with different functions are released into the blood. These hormones include CCK, GLP-1, bombesin or gastrin-releasing peptide, PYY, ghrelin, enterostatin, glucose-dependent insulinotropic polypeptide (GIP), pancreatic polypeptide, and somatostatin. From this series of hormones, CCK, GLP-1, and bombesin have a direct effect on gastric emptying (51, 56), whereas the others are supposed to have longer-lasting postprandial effects on satiety and meal initiation (57–59).

Cholecystokinin

The most widely investigated gut hormone in relation to appetite is CCK. CCK is released in the blood as a function of the presence of fat (ie, long-chain free fatty acids) or protein (ie, amino acids) in the duodenum, where CCK has an effect on

receptors of the nervus vagus (56). The nervus vagus transports the signal to the nucleus tractus solitarius in the brainstem and from there to the CNS (19).

Most studies on CCK follow a particular design in line with its presumed mode of action. In general, exogenous or endogenous CCK is infused or produced, and, during the same time, ad libitum food intake or subjectively rated appetite is measured. Outcome measures are the amount of food ingested, subjectively rated appetite, or both. Endogenous CCK production is often induced by oral or intraduodenal admistration of fat or protein. In some studies, specific CCK receptor blockers (eg, loxiglumide) are administered to investigate the mechanism by which CCK exerts its action.

The first report of the appetite-suppressing effect of CCK in humans is a study by Kissileff et al (60) showing that the exogenous, peripheral (intravenous) administration of high nonphysiologic doses of CCK suppressed food intake in a test meal in humans by 19%. Since that study, there have been many studies of the effect of CCK on appetite (eg, 61–72; *see* Table 1 under "Supplemental data" in the current issue at www.ajcn.org). Overall, these studies give a fairly consistent picture of the effect of CCK on appetite. The weighted average of intake suppression in the first 10 studies (total $n = 214$ subjects; *see* Table 1 under "Supplemental data" in the current issue at www.ajcn.org) that compared the effects of exogenous CCK and saline on actual food intake is 22.5%. Two studies showed a dose-dependent effect of CCK on appetite (73, 74). Depending on the dose, subject characteristics, and other experimental conditions, intake suppression varied between 0% (74) and 63% (73).

A full stomach (after preloads of ≈400–500 mL) is a necessary condition for the appetite-suppressing effect of CCK. This indicates that the mechanism by which CCK suppresses appetite is the delay of stomach emptying (52). In a recent publication, Kissileff et al (75) show that CCK's suppression of food intake is enhanced when the stomach is distended.

Studies on endogenously produced CCK also show that CCK acts as an appetite suppressant, although this effect is not clear from all studies (76–78). An elegant study by Maztinger et al (79) showed that the satiating effect (of intraduodenal administration) of fat could be counteracted by a specific CCK receptor blocker, loxiglumide. This finding implies that CCK mediates the effect of fat on satiation (ie, meal termination; *see* Table 1 under "Supplemental data" in the current issue at www.ajcn.org).

The effects of CCK on subjectively rated appetite are less clear than are the effects of CCK on food intake. All of the 16 studies on the effects of CCK or CCK blockers on food intake indicated that CCK suppressed food intake. The effects of CCK on subjectively rated appetite were apparent in only 8 of the 17 studies that included subjective ratings of appetite, which is probably related to the higher degree of random or systematic error in measures of subjective ratings than in measures of food intake. These bigger error components with subjective ratings imply that a larger number of subjects is needed to show systematic effects (10).

The results of the studies of CCK show that CCK can be used as a biomarker of satiation. Both endogenous and exogenous CCK suppresses appetite, and higher concentrations of CCK produce larger appetite-suppressing effects. CCK has an important role in the causal chain leading to satiation or meal termination. Observations from other studies have shown, for example, that fats with long-chain fatty acids result in higher CCK concentrations than do fats with short-chain fatty acids (80, 81). Hall et al (82) recently reported on a study in which they showed that casein and whey proteins exert different effects on CCK, GLP-1 release, and appetite. These studies imply that (ingredients of) foods that have a high potency for releasing CCK may be used to produce foods with a higher satiating effect. This observation creates a major and exciting challenge for future research.

One of the limitations of the role of CCK as a biomarker is the technical difficulty of its quantitative assessment in blood. Attemps to develop a radioimmunoassay for CCK had to overcome numerous challenges, such as the multiple molecular forms of CCK, low concentrations, and an amino acid sequence similar to that of gastrin (83). Plasma concentrations of gastrin are 20–100 times higher, so that even slight antibody cross-reactivity with gastrin poses a substantial problem for the accurate measurement of blood concentrations of CCK (83). Accordingly, the sensitivity and specificity of an accurate CCK assay must be extremely high (83).

Glucagon-like peptide 1

GLP-1 is produced primarily in the ileum (84) in response to the presence of nutrients, ie, carbohydrates and fat (85). GLP-1 stimulates the islet β cells in the pancreas to secrete insulin, thereby contributing to the lowering of the blood glucose concentrations in response to carbohydrate ingestion (84). GLP-1 is thought to play an important part in the "ileal brake" mechanism (ie, adjustments of stomach and gut motility after food ingestion) that causes a moderate and stable (digestible) flow of nutrients from the stomach into the small intestines. This is probably also the mechanism by which GLP-1 exerts its effect on appetite (86). It is important to notice that the biologically active form of GLP-1, GLP-$1_{(7–36\ amide)}$, is rapidly degraded by the enzyme dipeptidyl peptidase IV to the inactive form GLP-$1_{(9–36)}$ (87).

The first report of the effect of GLP-1 on human appetite comes from Flint et al (88), who showed that the exogenous intravenous infusion of GLP-$1_{(7–36\ amide)}$ reduced the ad libitum energy intake from a test meal in 20 nonobese men by ≈12%. During GLP-$1_{(7–36\ amide)}$ infusion, hunger and prospective food consumption were lower than during saline infusion (*see* also 89–93; *see* Table 2 under "Supplemental data" in the current issue at www.ajcn.org).

A published meta-analysis of 115 subjects with respect to the effects of GLP-$1_{(7–36\ amide)}$ infusion on ad libitum energy intake during test meals showed an intake reduction of 12% during GLP-$1_{(7–36\ amide)}$ infusions but none during saline (control) infusion. Reductions were similar for obese (9%) and nonobese (13%) subjects (94). An interesting finding in this meta-analysis was that differences between blood GLP-$1_{(total)}$ (ie, the sum of biologically active and nonactive forms) concentration during placebo and GLP-$1_{(7–36\ amide)}$ infusion ($n = 43$ subjects) were negatively correlated with differences in ratings of prospective consumption ($r = -0.43$) and hunger ($r = -0.26$) and positively correlated with differences in fullness ratings ($r = 0.38$; 94).

GLP-1 reduces appetite in normal, obese, and diabetic subjects. The study by Gutzwiller et al (95) clearly suggested a dose-response effect in the appetite-suppressing effect of GLP-1

because the most effective suppression was found at concentrations slightly above normal physiologic concentrations (51, 95; *see* Table 2 under "Supplemental data" in the current issue at www.ajcn.org).

The effect of GLP-1 on meal size is a typical short-term effect, and in animals the effects of GLP-1 on energy intake reduction were shown to be effective in the short term but not in the long term. However, a recent 6-wk study with human diabetic patients showed that continuous subcutaneous infusion of GLP-$1_{(7–36\ amide)}$ reduced appetite and body weight (86). The rapid degradation of GLP-$1_{(7–36)}$ in GLP-$1_{(9–36)}$ could explain why continuous infusion of GLP-$1_{(7–36\ amide)}$ exerts long-term effects on appetite, whereas a bolus or endogenous release of GLP-$1_{(7–36\ amide)}$ exerts short-term effects on meal size and appetite.

Studies of endogenous stimulation of GLP-1 production under the influence of different nutrients (eg, glucose and fructose) have not yet reached the same level of progress as have studies of CCK and fat. Oral glucose has a bigger effect on GLP-$1_{(total)}$ release than does fructose, but glucose and fructose have similar effects on appetite (96).

In summary, studies of GLP-1 show that it may be used as a biomarker of satiation. GLP-1 measures are feasible, valid, reproducible, sensitive, and specific. GLP-1 is likely to be a causal factor in the process of satiation. Food intake and subjectively rated appetite decrease as a function of GLP-1 administration. However, little is known about the possible effects of foods, which may have different satiation efficiencies through differential effects on GLP-1 production. Answering these questions may be a challenge for future studies.

Bombesin and gastrin-releasing peptide

Bombesin, isolated from the skin of the European amphibian *Bombina bombina*, and its mammalian counterpart gastrin-releasing peptide (GRP) are neurotransmitters involved in several gastrointestinal functions, among them stimulation of CCK release and antrum and pyloric contraction. These effects are related to the fact that bombesin can inhibit gastric emptying in humans (97).

Lieverse et al (98–101) conducted most of the studies of the effects of bombesin on hunger and satiety in humans in the mid-1990s. In an early study, they showed that mean (±SEM) test meal (ie, banana) intake in 9 lean men was 482 ± 74 g during bombesin infusion and 602 ± 68 g during saline infusion (98). Infusion of bombesin in combination with loxiglumide, a CCK receptor blocker, resulted in a similar suppression of food intake, which shows that the appetite-suppressing effect of bombesin is independent of the presence of CCK. The results of subjective ratings of hunger and satiety were in line with the food intake data. The independence of the appetite-suppressing effect of bombesin from CCK was confirmed in a later study (99).

The appetite-suppressing effects of intravenous infusions of bombesin and GRP in humans were also shown by Muurahainen et al (102) and Gutzwiller et al (103). Lieverse et al (100) compared the effects of bombesin and saline infusion in 9 obese women and 9 lean women and found that test meal intake was significantly reduced in the lean subjects (bombesin: 294 ± 55 g; saline: 467 ± 69 g) but not in obese subjects (bombesin: 431 ± 60 g; saline: 499 ± 99 g). Subjective ratings of hunger and satiety were in agreement with this finding. The lower sensitivity of obese subjects than of lean subjects to the appetite-suppressing effect of bombesin was confirmed in a second study (101).

The results of studies of bombesin suggest that GRP may be an interesting biomarker for satiation. However, the number of human studies is very limited, and there are no data on how various nutrient loads may affect GRP concentrations. More research is needed to establish whether GRP is a useful biomarker in appetite research.

Somatostatin

Data on human appetite in relation to other gastrointestinal hormones involved in meal termination are limited. In a study in 10 humans by Lieverse et al (104), intravenously infused somatostatin was shown to suppress food intake and feelings of hunger. Lavin (105) found that, under hyperinsulinemic, euglycemic conditions, intravenous infusion of the somatostatin analogue octreotide suppressed the release of GIP and GLP-1 and the corresponding rise in insulin induced by intraduodenal glucose infusion. Moreover, octreotide reversed the suppression of appetite and the reduction in energy intake induced by intraduodenal glucose infusion (105). These were the only human studies of somatostatin in relation to appetite that we found.

PERIPHERAL AND CNS MARKERS INVOLVED IN SATIETY

In general, it is assumed that people start eating when they get hungry. However, meal initiation does not depend only on internal factors. Environmental cues related to the time of the day or food cues and social events are also important triggers of the next eating moment (5–7).

In many of the studies discussed below, environmental factors are kept constant. In some of these studies (*see* below for specific references), subjects are even isolated from time cues, so that the focus of the study is on the internal signals that drive meal initiation and satiety. In others of these studies, the time between the preload and the next spontaneous eating moment is defined as the measure of satiety.

BIOMARKERS OF SATIETY AND MEAL INITIATION IN THE CNS

There are 4 PET and 2 fMRI studies on brain activity related to hunger and satiety (106–110). In the PET studies, the state of extreme hunger (36-h fast) was compared with the state of extreme fullness (≈30 min after the beginning of ingestion of a test meal containing 50% of the estimated 24-h energy expenditure). In the fMRI studies, subjects who fasted overnight ingested 75 g glucose dissolved in 300 mL water while they were undergoing scanning (*see* Table 3 under "Supplemental data" in the current issue at www.ajcn.org).

The PET studies highlighted a large number of areas in which the rCBF, a marker of neuronal activity, differed between the state of hunger and that of satiety. Among others, satiety was associated with increased rCBF in the prefrontal cortex (PFC). This is an area known to exert an inhibitory control on brain activation in response to external and internal stimuli (111–113). It has efferent projections to limbic and paralimbic areas, which are involved in drive-related and emotional behaviors. It is interesting that subjects with impaired PFC function suffer from hyperphagia (114). Therefore, it has been postulated that the activation of the PFC in response to a meal contributes signifi-

cantly to the onset of satiety (106–109).

The rCBF in the hypothalamus [an area known to be involved in the regulation of food intake (115, 116)], the hippocampus (memory function), the thalamus (an area that integrates and relays sensory information to the cortex), and the insular and temporal cortex (both areas deal with gustatory sensory information), which are all limbic or paralimbic areas, was lower in the satiety condition than in the hunger condition (106–109). There were also consistent decreases in rCBF in the caudate nucleus and cerebellum, which are involved in motor activity. The relation of these changes to hunger and satiety is not yet clear. In the reports cited, there were no comments on these findings.

After the brain's responses to food in general were mapped, investigators began to investigate differences between obese and nonobese subjects. In response to satiety, both obese men and women were reported to have greater increases in the rCBF in the PFC but greater decreases in the rCBF in the orbitofrontal and temporal cortex than do their lean counterparts (107, 108). Obese and lean women also differed with respect to the association between changes in plasma glucose and free fatty acids and the amount of rCBF in the PFC (108). This, again, pinpoints the PFC as an area that reflects differences in the response to satiety of obese and nonobese subjects.

Common fMRI study design and analysis are not very well suited to the use of food stimuli, because of the problems associated with head movement and the unknown timing of the brain's response to such a stimulus. From this perspective, it is interesting to note the work of Matsuda et al (117) and Liu et al (110), who showed that, by using BOLD fMRI, it is possible to measure spatial and temporal characteristics of the brain's responses to food stimuli. Both studies reported a decrease in BOLD signal in the hypothalamus ≈10 min after the subject began drinking a glucose solution (110, 117). It is interesting that Matsuda et al (117) found that this inhibitory response was delayed as well as attenuated in obese subjects. Furthermore, Liu et al (110) reported that this hypothalamic response to a glucose load was negatively correlated with fasting plasma insulin concentrations.

In summary, these functional neuroimaging studies are exciting developments in the study of the mechanisms involved in the regulation of appetite. To date, the focus in the PET studies was on the comparison between extreme hunger and extreme fullness, which includes more sensations than simple common feelings of hunger. The temporal (1 scan/8 min) and spatial (5 mm) resolutions of PET are too low to be used for measuring brain responses that could serve as biomarkers of meal initiation. This would require a temporal resolution of much less than 1 min, as is clear from data for glucose (*see* below). The spatial resolution is also too low to detect meaningful changes in the different loci of the hypothalamus, which are strongly involved in hunger and satiety. These spatial and temporal limitations make it unlikely that PET scan techniques will soon be used for measuring biomarkers of satiety or meal initiation (112).

The use of fMRI to study CNS effects of food stimuli has proven to be particularly useful for taste and odor (41), but the data with respect to hunger and satiety are limited. The studies of Matsuda et al (117) and Liu et al (110) are promising, but they require replication by other research groups.

BIOMARKERS OF SATIETY AND MEAL INITIATION IN THE PERIPHERAL PHYSIOLOGY

Physical measures

At first sight, body temperature and diet-induced thermogenesis (DIT) seem to be attractive candidates for use as biomarkers involved in the satiety process. Heat production and the loss of heat during the oxidation of macronutrients may serve as integrative measures of energy, nutrient balance, or both. In the theory of Friedman (118), hunger depends on the amount of oxidative phosphorylation and ATP production in the liver. Thermogenesis partly reflects this level of oxidation (118). This idea is in line with observations from Westerterp-Plantenga (119), who showed that, under conditions of low oxygen availability such as high altitudes, humans have a low appetite.

Diet-induced thermogenesis

As far as we are aware, 5 studies in humans have investigated the relation between DIT and appetite. Raben et al (120) found that differences in 6-h postprandial DIT and satiety in 10 men were positively correlated after isoenergetic meals with different amounts of fiber. Westerterp-Plantenga et al (121) observed a positive relation with a correlation coefficient of ≈0.2 between DIT and satiety after lunches with different proportions of fat and energy in 32 men and women. Crovetti et al (122), studying 10 women, and Westerterp-Plantenga et al (123), studying 8 women in a respiratory chamber, found that DIT after protein-rich meals was higher than DIT after carbohydrate- or fat-rich meals. In both studies, higher DIT was correlated with higher satiety and lower hunger ratings. However, in the study by Crovetti et al, differences between protein and carbohydrate or fat DIT only emerged >3 h after ingestion of the preloads (122). This is a time span in which differential effects of macronutrients on appetite have disappeared (124). Another issue is that DIT and satiety after a meal are not synchronous over time (123), which makes it difficult to accept DIT as a causal factor for satiety.

In the fifth and most recent study on the relation between DIT and appetite, Raben et al (125) found that alcohol and protein produced larger effects on thermogenesis than did carbohydrates and fats. However, there were no significant differences in rated appetite and food intake after the ingestion of amounts of these macronutrients with equal energy. These data do not support the proposed relation between the macronutrient oxidation hierarchy and the satiety hierarchy (125).

DIT measurements are not easy to carry out; they require facilities for indirect calorimetry, such as respiration chambers, ventilated hoods, or both. With the ventilated hoods, DIT measurements require subjects to sit still for several hours, whereas, in respiration chambers, subjects may move as they wish, which increases random error in DIT measurements. Differences between the DIT values of different macronutrients are difficult to assess, and the relation between DIT and appetite has not been determined. These observations make DIT measurements unattractive candidates for biomarkers of satiety.

Body temperature

The effects of body temperature on appetite have not been studied in great detail. The common-sense observation that fever reduces appetite may indicate that a higher body temperature is

related to a low appetite. A recent study by Westerterp-Plantenga et al (126) found that a low ambient temperature was associated with a lower body temperature and a higher ad libitum food intake.

At present, because of a lack of data, body temperature measurement cannot be used as a biomarker of satiety. Body temperature measurements at various places of the body, eg, in the neighborhood of the liver, may be relatively easy to obtain with the use of infrared scanning techniques (127, 128). Therefore, from a theoretical and practical perspective, this might be an interesting area for future research.

Hormonal and biochemical measures

Glucose

Glucose uptake and use have long been central features of many hypotheses about meal initiation because of the central role of glucose in the regulation of energy metabolism, which is due to its exclusivity as an energy source for the CNS, its limited storage, its high turnover rate, and its tight regulation (129). In the 1950s, Mayer (129) proposed the glucostatic theory for short-term appetite regulation, which postulated that glucoreceptors in the brain detect changes in the rate of glucose utilization. A decrease in glucose utilization represented the stimulus for meal initiation, and an increase in glucose utilization represented the onset of satiety.

The clamp studies of Gielkens et al (130), comparing 5 mmol and 15 mmol glucose; of Chapman et al (131), comparing 5 mmol and 12 mmol glucose; and of Andrews et al (132), comparing 4 mmol and 8 mmol glucose, suggest slightly but not consistent lower hunger levels at higher glucose concentrations. Glucoprivation induced by intravenous infusion of 2-deoxy-D-glucose, which competitively inhibits intracellular glucose utilization, induces hunger (133, 134) and thirst in humans (134). Lavin et al (135) showed that intraduodenally administered glucose reduced subsequent energy intake ≈20% more than did intravenously administered glucose. Hunger ratings were lower and fullness and satiety were greater with intraduodenal glucose more than they were with intravenous glucose (135). These appetite-suppressing effects of intraduodenal glucose were abolished by the infusion of octreotide, a somatostatin analog that inhibits gut hormone secretion. These results indicate that the effects of intestinal glucose on food intake and appetite are not regulated by increased blood glucose concentrations. Lavin et al (135) argued that these effects are more likely to be induced by small-intestine stimulation of glucoreceptors or osmoreceptors, which may induce satiety through either direct vagal stimulation or the release of insulin, incretin peptides, or both. In summary, there is some evidence that high blood glucose concentrations are associated with lower appetite, but this relation is weak (*see* Table 4 under "Supplemental data" in the current issue at www.ajcn.org).

Other research has shown that, instead of the absolute concentrations of blood glucose, the decreases in glucose utilization or intracellular glucose concentration act as the stimulus for meal initiation. This idea is in line with the original glucostatic theory of Mayer (129). Louis-Sylvestre and Le Magnen (136) were the first to find that, in rats, meal initiations were preceded by a transient decline in blood glucose, starting 5–6 min before meal onset. In humans, declines in blood glucose also seem to precede meal requests (137; *see* Table 4 under "Supplemental data" in the current issue at www.ajcn.org). A distinction is made between transient and dynamic declines. The endogenous transient decline in blood glucose is defined as a deviation of >5% from a stable baseline blood glucose concentration that lasts ≥5 min. A dynamic decline is a rapid drop in blood glucose after a rise induced by the ingestion of a drink or a meal (138). There is a high correlation between dynamic and transient declines in blood glucose and meal requests (138–140). The strong association between meal requests and declines in blood glucose seems to disappear when subjects are in a negative energy balance. In one report, subjects also had meal requests when their blood glucose concentrations were stable (141).

One other possible way of investigating the relation between blood glucose concentrations and satiety is with the help of foods with different types of carbohydrates, because the postprandial response of blood glucose differs between carbohydrates (142). However, it should be realized that incretin hormones, vagal stimulation, and other metabolic processes mediate the blood glucose response to foods (143). The glycemic index (GI) of a carbohydrate reflects the postprandial glucose response after consumption of a standard amount of carbohydrate from a test food in comparison with the postprandial responses after consumption of a control food (either glucose or white bread) (142). It could be hypothesized that high-GI foods would lead to steep rises in glucose and related steep rises in satiety and subsequent steep decreases in satiety, and that lower-GI foods would lead to a more stable pattern of glucose concentrations and satiety (144–146). However, the results of studies are yet ambiguous. Some investigators found no effect of GI on food intake and appetite (96), while others found a stronger suppression of hunger and energy intake after consumption of carbohydrates with a low GI (147–149). A recent study by Anderson et al (150) showed a higher short-term (≤1 h) appetite-suppressing effect of high-GI foods than of low-GI foods.

The results of the studies of glucose show that glucose may be used as a biomarker of satiety (meal initiation) in certain conditions. It is clear that absolute glucose concentrations have no straightforward relation to appetite. Transient and dynamic declines in blood glucose concentrations within a short time frame (5 min) are strongly related to meal initiation. These observations imply that meal initiation can be postponed by delaying transient or dynamic declines in blood glucose. It is not clear how this can be achieved in relation to the carbohydrate structure of foods, but that could be an interesting subject of future research. The measurement of small declines in blood glucose concentrations within a short time is not easy and is rather invasive, because blood glucose has to be measured continuously (ie, 8–10 times/min), which is not feasible in many situations.

Insulin

Insulin, which has also been implicated in the long-term regulation of energy balance (151), is produced in the β cells of the pancreatic islets and secreted in the blood in response to small increases in blood glucose concentrations. In healthy subjects, it stabilizes blood glucose by stimulating the uptake of glucose by peripheral tissues and by suppressing hepatic glucose production. The insulin response to a meal is also mediated, in part, by the insulinotropic incretin hormones GLP-1 and GIP, which are secreted from endocrine cells in the intestinal mucosa. Incretin hormones enhance insulin secretion in excess of that elicited by the absorbed nutrients themselves.

Studies with exogenous insulin give mixed results. An early

clamp study by Rodin et al (152) in 20 subjects found that high insulin concentrations, independent of changes in blood glucose, increase hunger ratings and fluid intake (8). However, results of the studies of Woo et al (153), Gielkens et al (130), Lavin (105), and Lavin et al (135) suggest that under euglycemic or hyperglycemic conditions, or both, insulin does not affect food intake or appetite (*see* Table 5 under "Supplemental data" in the current issue at www.ajcn.org).

Studies of the effect of endogenous insulin on food intake and subjective satiety and food intake suggest that insulin has an appetite-suppressing effect in lean subjects but less so in obese subjects. Holt et al (147) found that the insulin response (AUC) was negatively correlated ($r = -0.40$) with energy intake in a subsequent ad libitum test meal. Results from a study of 6 lean and 6 obese men conducted by Speechly and Buffenstein (154) showed a negative correlation between insulin concentrations and subsequent food intake in lean men, but not in obese men. A similar finding was reported by Verdich et al (155) in 12 lean and 19 obese men.

It could be argued that the negative relations between endogenous insulin concentrations and both food intake and subjective appetite are the result of changes in substances other than insulin. It could be that glucose plays a role here because, in studies where glucose concentrations were kept constant, there was no effect of insulin on appetite and food intake (130, 135, 153). However, from the previous paragraph on glucose, it is apparent that absolute glucose concentrations do not relate strongly to appetite. An alternative explanation for the abovementioned negative relations is that the release of incretin hormones after food intake and the subsequent release of insulin may explain why endogenous insulin concentrations do correlate with appetite and energy intake, whereas exogenous insulin concentrations do not correlate with appetite and energy intake.

Fasting insulin concentrations during energy restriction decrease (156–158). The relation between these fasting insulin concentrations and increases in appetite or food intake are not clear yet. Heini et al (157) found no relation between fasting insulin concentrations and appetite ratings in obese women at weeks 3 and 5 of an energy-restricted diet, whereas Mars et al (159) found a correlation ($r = -0.41$, $P < 0.01$) after 2 d of energy restriction that disappeared after 4 d of energy restriction ($r = -0.19$, NS) in a group of lean and overweight men.

Altogether, it seems improbable that insulin can act as a biomarker of satiety. There is no straightforward relation between blood insulin concentrations and appetite because that relation is confounded or moderated by many metabolic processes. The effects of glucose and incretin hormones on insulin concentrations and the effect of obesity on the relation between insulin concentrations and appetite illustrate this. Insulin plays such a central role in the energy metabolism that it cannot be a specific biomarker of satiety.

Leptin

Leptin, the product of the *ob* gene, is synthesized mainly by adipose tissue, provides information on the availability of body fat stores to the hypothalamus. The studies in animals that described its discovery (160, 161) showed that leptin reduces food intake and body weight. Plasma leptin concentrations in humans correlate positively with the total body fat stores (162, 163).

When humans are in energy balance (ie, weight-stable during the studies), the relation between leptin concentrations and food intake and appetite is not clear. In general, leptin concentrations do not change acutely (ie, within 3–4 h) in response to meals, and most studies find that there is no relation between leptin concentrations and subjective measures of appetite before and after meals (164–166). Hunger ratings change dramatically after a meal, and thus there cannot be a strong direct relation between hunger ratings and leptin concentrations.

A study by Chapelot et al (167) in 6 lean men did find strong negative correlations ($r = -0.95$, -0.85) between leptin concentrations before lunch and dinner and the energy intake during the first course of these meals. However, changing leptin concentrations in this study were tied to the diurnal rhythm of leptin (165, 168). In the study of Chapelot (167), it was the leptin concentration in relation to the baseline in each subject that predicted food intake. This finding relates to the rhythmicity in leptin signaling to the brain that may play an important role in predicting appetite and energy intake (169).

Energy deficits of >24 h lead to decreases in plasma leptin concentrations (163, 170–175), whereas an energy surplus of >24 h results in increased leptin concentrations (175, 176). Plasma leptin is strongly negatively correlated with appetite and food intake when the energy balance is distorted (171–173, 175). The association between leptin and appetite after energy restriction is independent from fat mass, which indicates that the low leptin concentrations are instrumental in restoring energy balance (171). Two intervention studies, in which 30 (177) and 12 (178) obese men following a weight-loss regimen were given pegylated human recombinant leptin also showed that leptin reduced appetite.

In the study by Chin-Chance et al (175), changes in baseline leptin values after 72 h of overcaloric, undercaloric, or eucaloric feeding were found to predict subsequent ad libitum intakes at breakfast ($R^2 = 0.41$). However, in this regression equation, each of the 6 participating subjects was represented 3 times. Because these measurements are dependent on each other, it is difficult to take this study as conclusive evidence for the role of leptin in the restoration of energy balance.

It is interesting that the results of a recent study by Weigle et al (179) suggest that a low-fat, high-carbohydrate ad libitum diet accompanied by weight loss leads to lower leptin without an increase in appetite. The authors attributed this effect to an increased leptin sensitivity during the low-fat, high-carbohydrate diet. In this study, the proportional amplitude of the 24-h leptin profile was increased after 12 wk on the 15% fat diet. This increase in amplitude was strongly negatively correlated to the percentage change in body weight and body fat (179).

In summary, leptin is negatively correlated with appetite and food intake when subjects are not in energy balance, whereas the relation between leptin and appetite during energy balance is less straightforward. Therefore, leptin seems to have a role in the regulation of food intake when energy stores change. This is confirmed by Mars et al (159), who found a stronger negative correlation between leptin and appetite ratings after 2–4 d of 66% energy restriction than before the energy restriction protocol. Thus, leptin is suitable as a long-term biomarker of satiety when subjects are not in energy balance. However, leptin cannot serve as a simple short-term biomarker of satiety.

Glucose-dependent insulinotropic polypeptide

GIP is released not only in response to glucose ingestion, as its name suggests, but also in response to fat ingestion (180). It

shares with GLP-1 its insulinotropic effect. Few studies have investigated GIP responses in relation to appetite. In a study by Verdich et al (155), GIP responses to a fixed preload (2.5 MJ) were inversely correlated with energy intake at an ad libitum test meal 3 h after the preload. This finding was consistent across a group of 12 lean subjects and a group of 19 obese subjects.

Although this study by Verdich et al suggested a role for GIP in human appetite regulation, a study by Vozzo et al (181) presented data that do not support that idea. Vozzo et al studied in 20 subjects the effects of 300 mL water, 75 g glucose/300 mL water, and 75 g fructose/300 mL water on GIP concentrations and on ad libitum test meal intake 3 h later. They found that that glucose and fructose were equally effective in suppressing food intake in the test meal, but there were large differences in GIP concentrations after glucose and fructose ingestion. This finding does not support a major role for GIP in appetite regulation.

Ghrelin

Ghrelin is abundantly synthesized in the fundus of the human stomach (182) and also in other tissues and other parts of the gastrointestinal tract (183). Ghrelin is the endogenous ligand for the growth hormone secretagogue receptor (184) and therefore stimulates the release of growth hormone.

The results of recent studies on ghrelin suggest that it may serve as an excellent biomarker for satiety. People with the Praeder-Willi syndrome, which is characterized by severe hyperphagia, have 4.5 times higher ghrelin concentrations than do equally obese controls (185). In another study with 7 subjects with Praeder-Willi syndrome after an overnight fast and 5 control subjects after a 36-h fast, subjective hunger ratings were significantly correlated with ghrelin concentrations ($R^2 = 0.50$; 186). Intravenous infusions of ghrelin in 9 healthy humans were shown to potently enhance subjectively rated appetite and to increase energy intake during lunch by 28% (187). Diurnal rhythms in ghrelin concentrations before and after weight loss concur with diurnal rhythms in appetite in humans (58, 188, 189). On average, ghrelin concentrations were 24% higher when obese subjects lost 17% of their initial weight (189). Ghrelin concentrations decline quickly after each meal, returning to premeal concentrations before the next meal is initiated (58). Plasma ghrelin concentrations in normal-weight subjects decrease after oral and intravenous administration of glucose, but the intake of an equivalent volume of water does not influence ghrelin concentrations (190), which suggests that ghrelin secretion is not affected by stomach expansion. In a recent study, Blom et al (191) found that different carbohydrate preloads, in proportion to their energy content, suppressed ghrelin concentrations in humans. Ghrelin concentrations were strongly inversely correlated ($r < -0.80$) with subjective appetite ratings. However, the infusion of lipids or the ingestion of a high-fat diet does not suppress the postprandial ghrelin concentrations as effectively as does the infusion or ingestion of glucose-containing carbohydrates (179, 192). Fat restriction seems to avoid the increase in ghrelin concentrations caused by dietary energy restriction (179).

The data so far on ghrelin are very exciting, because there appears to be a close correspondence between ghrelin concentrations and appetite. Ghrelin is one of the first hormones that has a stimulating effect on appetite, and it seems to work both in the short term with meal initiation and in the longer term after weight loss.

Peptide YY

PYY is released primarily from the distal gastrointestinal tract, ie, the colon, and acts as an agonist (stimulator) on the Y2 receptor in the hypothalamus. This receptor inhibits the release of neuropeptide Y, the most potent CNS stimulant of appetite (57).

In 2 recent studies, intravenous infusion of exogenous $PYY_{(3–36)}$ (the biologically active form of PYY) was shown to suppress 24-h food intake in humans (57, 193). Subjective ratings of hunger and satiety were in line with the lower food intake (57, 193). In both obese and lean subjects, food intake during a buffet lunch was decreased by ≈30% (193). Endogenous fasting and postprandial concentrations of $PYY_{(total)}$ (the sum of biologically active and nonactive forms) were significantly lower in obese subjects than in lean subjects, and fasting concentrations of $PYY_{(total)}$ were negatively associated with BMI ($R^2 = 0.71$; 193). MacIntosh et al (85) studied the effects of intraduodenal infusion of lipids and glucose on the release of gastrointestinal hormones and subjectively rated appetite in young and elderly subjects. There were significant positive correlations during lipid infusion between changes in plasma $PYY_{(total)}$ concentrations and changes in fullness rating in both young ($R^2 = 0.29$) and elderly ($R^2 = 0.29$) subjects. Similar results were obtained during glucose infusion. Other studies have shown that PYY is also released in response to carbohydrate-, protein-, and fat-rich meals, although not after an equal volume of water (194, 195) or fat replacers (196).

The studies of Batterham et al (57, 193) found that exogenous infused $PYY_{(3–36)}$ exerts a suppressive effect on food intake, which shows that PYY is one of the causal agents in the appetite cascade. However, data on the relation between PYY and appetite are still very limited. Much more work seems necessary before PYY can be said to serve a biomarker of satiety.

Enterostatin

Enterostatin is a gastrointestinal peptide that, according to data from animal studies, is hypothesized to be involved in the regulation of fat intake, the preference for food with a high fat content, or both (197). Three studies investigated the effect of enterostatin on appetite and food intake in humans, one of which used intravenous administration (198), and the other 2 of which used oral administration (59, 199). None of the 3 studies found an effect of enterostatin on ad libitum food intake.

DISCUSSION

This overview of studies shows that a number of physiologic measures are available that can serve as biomarker of satiation, satiety, or both. With respect to satiation (meal termination), physical and chemical measures of stomach distension and blood plasma concentrations of CCK and GLP-1 are useful. With respect to satiety and meal initiation, glucose dynamics within a short time frame (<5 min), leptin concentrations during longer-term negative energy balance (>2–4 d), and ghrelin concentrations at both the short-term and long-term intervals are physiologic markers. More work is needed to establish whether the other potential biomarkers of satiation, satiety, or both can be useful (Table 1).

Greater stomach fullness and higher concentrations of CCK and GLP-1 are associated with lower subjective hunger ratings and with lower food intake. These measures are also part of the

causal chain that leads to meal termination, which implies that they can be valid biomarkers of satiation. Measures of stomach fullness, CCK, and GLP-1 are feasible because they represent immediate outcome measures during the consumption of a meal. They are specific and sensitive because stomach fullness, CCK, and GLP-1 are different measures, but all 3 have a clear and straightforward relation with subjectively rated appetite and food intake. Reproducibility follows from the observation that different research groups report similar findings.

Absolute glucose concentrations do not relate to reported appetite; however, small declines within short time frames have been shown to relate to meal requests and reported hunger. This makes blood glucose dynamics an interesting biomarker for meal initiation and satiety. The frequent sampling (10 times/min) that is necessary and the required experimental control in these studies, such as time blinding and the long waiting times for subjects, make this technique less feasible for most research groups.

Whereas short-term glucose signals relate to appetite, leptin relates to long-term appetite. Leptin acts as a long-term signal that is instrumental to the restoration of energy balance after energy restriction. This makes leptin less feasible as a biomarker of short-term satiety, because the time needed to achieve an effect is not obtainable within or between meals. However, for long-term studies on energy balance, leptin may serve a very useful purpose—eg, to investigate the effect of different dietary regimens on long-term appetite responses. This might well be a fruitful area for future research, because the essence of the problem of obesity is the long-term energy balance. The observation in various studies that most dietary carbohydrates are more potent stimulators of leptin than is fat (165, 200) may offer an an explanation for the observation that high-carbohydrate, low-fat diets in humans lead to a lower ad libitum food intake and body weight (fat) than do low-carbohydrate, high-fat diets (201). The results of the studies of Weigle et al (179) and Chapelot et al (167) suggest a role for the relative changes (proportional amplitudes) in leptin during the day as an appetite signal to the brain (169).

Ghrelin is a hormone that acts in both the short term and the long term. From this perspective, ghrelin is one of the most exciting discoveries in appetite research in the past 5 y. The data so far suggest that ghrelin is an excellent biomarker for satiety. It acts as a peripheral hormone on receptors in the hypothalamus, thereby stimulating the expression of neuropeptide Y and agouti-related protein (202), which implies that ghrelin plays a causal role in the satiety cascade. Therefore, it can be a valid biomarker of satiety. Ghrelin's relations with hunger responses and food intake are also clear (185, 187, 189). It will be a challenge to investigate whether ghrelin is a functional hormone to restore energy balance after energy restriction, as well as to ascertain whether various ingredients or nutrients result in different ghrelin responses. The recent reports on PYY may indicate that PYY can serve as a biomarker of satiety (57). PYY acts as a peripheral signal on CNS receptors in the neuropeptide Y pathway, which gives it a clear role in the satiety cascade. It has also been shown to relate to subjective appetite and actual food intake. However, the data are still scarce, and thus it is too early to declare PYY a biomarker for satiety.

DIT and body temperature are dependent on nutrient oxidation and may therefore serve as an integrative measure of energy balance. From this perspective, they may be attractive candidates as biomarkers of satiety and satiation. However, DIT and satiety after meals are not synchronous over time (123). A recent study failed to show a clear relation between DIT and appetite (125). DIT is an integrative measure of oxidation of nutrients over the entire body, from head to toe. Such a measure seems not specific enough to be related to appetite. The same is true for whole-body temperature. This issue might be different if temperature measurements could be focused on the liver, which is the primary peripheral organ for the distribution of macronutrients.

In this review, we have referred to a number of physiologic measures that were investigated in relation to appetite. This list of measures is likely to expand in the near future. Chapelot et al (167) suggested that leptin acts on appetite through its effects on fatty acid concentrations. Fatty acid concentrations may also be an interesting candidate as a biomarker of satiety. Other biomarkers could lie in patterns in amino acid profiles in the blood, electrophysiologic recordings, and the discoveries of new hormones in relation to food intake.

CNS markers that have been investigated in relation to satiation reflect sensory-specific satiety, ie, the decline in pleasantness of a food during its consumption. This decline in pleasantness occurs within 2 min after the first bite, and thus it is probable that fMRI, which has a much higher time resolution (>10 scans/min) than do PET scans (1 scan/8–10 min), is a more suitable technique than is PET with which to assess this response. A similar notion applies for satiety responses: because hunger or satiety sensations can change very quickly, fMRI is more likely than is PET to play an important role in appetite research. An additional disadvantage of PET from an ethical point of view is its use of radioactive isotopes, which makes it a more invasive technique. Clearly, more quantitative data are needed to make these techniques suitable as biomarkers of satiation, satiety, or both.

In this review, we discussed ≈80 studies in which appetite was assessed by rating subjective feelings of appetite or by assessing food intakes in standardized settings. In almost all of these studies, these measures were in line with each other: that is, lower appetite ratings correlate with a lower food intake in a standardized setting. This observation reinforces the validity of the rating scales and the food intake assessment as a measure of appetite.

The major division between satiation and satiety, as described in this review, came from the model of Blundell (3) and Halford and Blundell (19), which helped to organize this complex area of food intake research. We decided to place several hormones, such as CCK and GLP-1, under the heading of satiation and another several measures, such as glucose, insulin, GIP, and PYY, under the heading of satiety. The distinction between satiation and satiety and the involvement of hormones in either meal termination, meal initiation, or both may not be as strict as suggested. For example, we believe that glucose and insulin in humans are mainly involved in satiety or meal initiation. However, Langhans et al (203) showed that glucose and insulin might also be involved in meal termination. The distinction that we made resulted from theoretical considerations and from the experimental designs in which the biomarkers were studied.

The next exciting challenge in this field is to find ingredients or specific fractions in foods that have a beneficial effect on these biomarkers. For the past 10–15 y, there has been an intensive discussion on the role of macronutrients in the regulation of energy intake and body weight (201). Now, more and more work seems to focus on specific kind of fats, carbohydrate, or proteins and their effect on physiologic measures that are causally related to energy and food intake. This development may help in the

design of foods that are beneficial in the regulation of food intake. We end this review by mentioning a few studies that focus on this new field of research. Two of these studies showed that long-chain fatty acids are more effective in releasing CCK than are short-chain fatty acids (80, 81). Hall et al (82) found that whey protein was more effective than was casein protein in the release of CCK and GLP-1 and the reduction of appetite. Data from Havel et al (200) suggest that high-fat diets lead to low circulating leptin concentrations, whereas carbohydrates were earlier shown to increase leptin concentrations (165). High-carbohydrate, low-fat diets may lead to a higher leptin sensitivity and therefore a lower ad libitum food intake and body weight (179). In this respect, Elliott et al (204) suggested that dietary fructose leads to lower insulin and leptin concentrations, which may contribute to an higher energy intake.

In summary, different amino acids, fatty acids, and carbohydrates have differential effects on the release of biomarkers of satiation and satiety. This is a very fruitful and exciting area for future research.

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