Deficits in gastrointestinal responses controlling food intake and body weight

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Obesity rates continue to increase throughout the world. The etiology of the disease is complex, involving a multitude of factors such as genetic, neural, physiological, hormonal, nutritional, social, and psychological, which can interact to promote weight gain under numerous conditions. Among these, a substantial body of evidence shows that overconsumption of highly palatable foods, such as those rich in fats, constitutes a major risk factor for the development of obesity (85, 172). Indeed, a strong correlation between total fat intake and obesity has been reported (26). Additionally, regular consumption of a diet high in fat content not only increases body fat stores but also raises the level of body fat the body regulates as normal, thus perpetuating obesity (240).

Although the contribution of dietary fat to obesity seems apparent, the control of fat intake is the least understood of the major macronutrients. Fat influences ingestive behavior at all stages from oral stimulation to long-term body-weight regulation (Fig. 1). Chronic exposure to a high-fat (HF) diet impacts parameters at any or all of several levels of control to result in obesity. This includes taste or other sensory qualities of HF foods, digestion and absorption of fats by the gut, generation and reception of meal-related and adiposity-sensing signals, and/or brain neurotransmitter systems that control food intake and metabolism. This review focuses on evidence demonstrating how chronic consumption of a diet rich in fats changes the gastrointestinal (GI) milieu and alters responses to satiation signals controlling food intake and regulation of body weight. Although several signals will be discussed, the review centers on the modulation of cholecystokinin (CCK) signaling, an important duodenal peptide, by dietary fat.

Digestive Functions Adapt to Chronic Consumption of Dietary Fats

The GI tract of omnivorous animals routinely encounters the three major macronutrient classes: proteins, carbohydrates, and fats. Thus the composition of the diet is often highly variable in terms of what proportion of intake is derived from a particular macronutrient class. Despite this, most often one particular macronutrient makes up the majority of foodstuffs presented to the gut. Consequently, some level of adaptation occurs within the GI tract to provide more efficacious metabolism or regulation of transport, digestive, and/or absorptive mechanisms.

Understanding the mechanism of adaptation to increased loads of dietary fat in the gut has been a subject of investigation for many decades. The identification of increased ileal absorption in response to large dietary loads of fat was one of the first discoveries of its kind to measure such changes (98). Singh and colleagues (198) identified increases in jejunal and ileal mucosal enzymes that paralleled an increase in lipid absorption in response to adaptation to an HF diet. Thus, rats maintained on a 45% vegetable oil diet for 4 wk had increased ileal uptake of oleic acid. This response was associated with mucosal hypertrophy, increased protein content, and overall intestinal mass (11). Additionally, Goda and Tskase (83) described shorter and thicker microvilli as well as more numerous enterocytes per villus in rats maintained on an HF (73% energy) diet for 7 days compared with controls receiving an equicaloric low-fat (LF) (7% energy) diet.

Adaptation by absorptive mechanisms is not limited to changes in brush-border morphology alone. Kalogeris and Painter (104) reported that plasma levels of apolipoprotein A-IV (apo A-IV), a lipid-responsive gut protein, initially increased to levels 40% higher than saline controls after lipid infusion. Interestingly, after 4 days of the procedure, apo A-IV...
plasma levels in triglyceride-fed animals decreased to values indistinguishable from control rats. These findings were attributed to paralleled increases and subsequent decreases of both pre- and posttranslational markers of apo A-IV secretion in jejunal tissue. Both rodent and human data suggest that intestinal apo A-IV synthesis and secretion are less responsive to fat following its chronic consumption (230). The relevance of these findings is significant in that it provides evidence for adaptive mechanisms that are able to quickly, in a matter of only a few days, return initially elevated apo A-IV plasma levels to normal in chronically lipid-infused animals.

Secretions from other alimentary organs, specifically the pancreas, are also subject to alterations in animals fed an HF diet. For example, when we adapted animals to LF or HF isoenergetic diets and measured pancreatic enzyme secretion using in vitro preparation assays, chronic ingestion of an HF diet decreased amylase secretion but increased absorptive capacity for fat and increased secretion of lipase for fat digestion (28). In vivo, pancreatic lipase has also been shown to adapt to changes in dietary fat intake by increasing enzyme synthesis in response to the amount of fat available and, to a lesser extent, differential fatty foods themselves (187). Changes like these enable an animal to take better advantage of a variable source of calories and represent a very simple system of an adaptive response to dietary changes. Spannagel et al. (205) showed that rats previously adapted to an HF diet had increased pancreatic exocrine secretion and plasma CCK release in response to triglyceride compared with unadapted rats infused with oleate. In humans, exposure to an HF diet also results in increased plasma CCK concentrations that could result in changes in sensitivity, secretion, and metabolism (67, 123). These findings point to increased efficiency of lipolysis via CCK response as...
a mechanism to increase effectiveness of fat absorption when dietary fat is presented to the gut in chronically high volumes. Collectively, these adaptive alimentary changes in response to increased proportions of fat, including increased fat absorption, may promote a more efficient process for energy metabolism from this rich source and may also lend to the storage of energy in the form of adipose tissue.

**HF Diets Diminish Appetite Responses to Lipids**

Nutrients in the intestine provide an array of signals that contribute to satiation. The presence of nutrients in the intestine and subsequent reduction in food intake in a dose-dependent fashion has been illustrated in a number of species including dogs (75), rhesus-monkeys (76), humans (231), as well as rats (88, 114, 180). Meyer and colleagues (145) experimentally perfused a variety of nutrients at differing doses in sham-fed and naturally fed rats. They found that sham-fed rats were more sensitive than naturally fed rats to lower doses of nutrient infusions, suggesting that meal termination signals elicited by intestinal nutrients can be more potent than those arising from gastric distension.

The magnitude of food-intake reduction varies with the type of nutrient being infused and caloric content of the infusate. Therefore, diminished sensitivity to caloric or nutrient-induced feedback signals may lead to overconsumption and subsequent weight gain. As such, obesity is often associated with reduced responsiveness to intraintestinal nutrients, especially fats. For example, obese Zucker (130), Otsuka Long Evans Tokushima Fatty (OLETF) (47, 193), Osborne-Mendel (OM) (87), and high-calorie-fed obese rats (210) have all been reported to be less sensitive to reduction of food intake by fats. Reduced sensitivity to the satiating effects of fats is also manifest in animals maintained on an HF, nonobesogenic diet. We and others have shown that both rats (50) and humans (25) eating HF diets exhibit reduced sensitivity to intestinal infusion of fats. Specifically, rats maintained on an HF (34% wt/vol) diet exhibit a significantly lower reduction of food intake after intraintestinal infusion of oleate compared with rats maintained on a LF (5% wt/vol), isocaloric diet (50) (Fig. 2A). In contrast, infusion of a carbohydrate solution suppresses food intake equally in both groups. This indicates that reduced sensitivity to the satiating effects of intraintestinal oleate appears to be related specifically to the high fat content of the diet and not to other dietary constituents. Similarly, Lucas and Sclafani (128) showed that in rats maintained on an HF diet (48% fat kcal) infusion of corn oil suppressed intake significantly less than equicaloric carbohydrate (Polyose) infusion. These results agree with several prior studies in humans showing that intragastric preloads of fat suppress subsequent test meal intake less than isocaloric carbohydrate preloads (73, 74).

The reduced satiating effects of fats observed during maintenance on an HF diet are not limited only to infusion studies or a single meal. To examine the effects of an HF diet on overall food consumption and meal patterning, Paulino et al. (169) measured meal frequency and size in freely feeding LF and HF diet-fed rats. They found that the inter-meal interval of HF-fed rats was significantly shorter than the LF-diet rats. Additionally, out of three primary meals consumed over 24 h, HF-fed rats ate significantly more of the second and third meals, resulting in a significant increase of daily food intake after only 4 wk on the diet. Thus the efficacy of GI responses to ingested fats to reduce food intake following prior adaptation to foods rich in fats is greatly diminished.

**HF Diet Alters Gastric Responses to Lipids**

Chronic consumption of an HF diet leads to metabolic changes, changes in GI functions such as motility, transit, gastric emptying, and secretion, as well as action of GI hormones (66). For example, intestinal transit is increased in response to intestinal infusion of lipids following exposure to fats (31). Work from our laboratory (46) demonstrated that the delay in gastric emptying of a saline load caused by intestinal oleate infusion is attenuated by prior adaptation to an HF diet in a dose-responsive manner, whereas the delay in gastric emptying caused by intestinal infusion of maltotriose (at caloric doses ~8× higher than the highest oleate dose) is unaffected (Fig. 2B). Similarly, in humans, subjects fed HF meals show an increase in gastric emptying rates in response to a fatty meal. By adapting normal weight subjects to an HF (4,603 kcal) or LF (2,151 kcal) diet for 2 wk, Cunningham and colleagues (52) found that gastric emptying and mouth-to-cecum transit time of an HF test meal were significantly faster.
in those maintained on HF diets than in those receiving the LF diet. In addition, the body weight of all subjects significantly increased during the 14 day HF diet compared with individuals on the LF regimen. Castiglione and colleagues (36) also reported that adaptation to HF diet accelerates gastric emptying of fat but not carbohydrate test meals in humans. In their study, subjects consumed a high-calorie (133% of normal), HF (55% energy) diet for 14 days. The HF, high-calorie diet produced a significant acceleration of gastric emptying during the linear phase and a trend toward acceleration in the lag phase of emptying of the HF test meal; however, there were no changes detected in the pattern of emptying of the high-carbohydrate test meal between groups.

To examine gastric emptying after diet adaptation, Boyd et al. assessed pyloric and duodenal motility in response to a 90-min duodenal lipid infusion in subjects adapted to either a 2-wk HF or high-carbohydrate diet (25). Their data suggest that subjects adapted to the HF diet experienced decreased pyloric and duodenal pressure, as well as increased hunger ratings, following the infusion relative to high-carbohydrate-adapted subjects. Food intake, however, was only reported in terms of “planned” dietary intake according to diet composition, and records during the adaptation period were not presented. Furthermore, the HF diet was not isocaloric with the LF diet, which may be confounding because of GI adaptations in response to increased caloric properties of diet, independent of composition. From these studies, it is difficult to assess whether or not the subjects were indeed adapted to these diets in the absence of corresponding dietary composition and intake data during the 2 wk before infusion testing. Also, a total of 134 calories over a 90-min period (1.5 kcal/min) were infused, which may have been insufficient to elicit GI effects indicative of real feeding load conditions. Despite these limitations, there is substantive evidence demonstrating that dietary manipulations alters GI responses in rodent models; however, human data remain scarce, and the relationship between dietary adaptation and gastric emptying still requires more experimental attention.

High Fat Reduces Neuronal Responses to Lipids

Intestinal fat reduces food intake and inhibits gastric emptying via vagal sensory neurons (95, 177, 191). Additionally, activation of intrinsic myenteric neurons participates in oleate-induced changes in GI motility (228, 229). Our laboratory (44) was the first to demonstrate that adaptation to an HF diet selectively reduces vagal and enteric neuronal sensitivity to intestinal oleate. The results revealed a significant decreased activation of neurons, measured by the presence of Fos-like immunoreactivity (Fos-Li) in the hindbrain, specifically in the nucleus tractus solitarius (NTS) and area postrema, as well as in the submucosal and myenteric plexus, following intraintestinal oleate infusion in HF diet-fed rats compared with their LF counterparts. However, in contrast to oleate infusion, maltotriose increased expression of Fos-Li in both diet groups with no significant differences between the diets. Furthermore, neuronal activation in the NTS was markedly reduced in response to a gastric gavage of 20% intralipid in HF-fed rats compared with LF-fed animals (169). These results demonstrate that reduced sensitivity to satiation and gastric inhibitory effects of oleate in HF-adapted rats may be mediated by the neural responses to intestinal stimulation of fats. Taken together, they provide evidence supporting the hypothesis that attenuation of nutrient-induced inhibition of food intake and gastric emptying may be attributable to diet-induced diminution of CCK responsiveness because intraduodenal oleate infusions activate intestinal vagal afferents via a CCK-mediated mechanism (106, 246–248).

High Fat Adaptation Diminishes Sensitivity to CCK

Gibbs, Young, and Smith (77) first discovered that exogenous administration of CCK causes a dose-dependent decrease in meal size. Subsequent studies have defined CCK as one of the most biologically potent satiety peptides in a variety of species, including humans and nonhuman primates (see Ref. 182 for review). As a satiety hormone, CCK acts to reduce food intake in response to intestinal nutrients, with highly specified effects on both fats and unhydrolyzed proteins (246). Established roles of CCK action include delay or inhibition of gastric emptying, promotion of secretion of bile into the intestinal lumen, and pancreatic enzyme secretion (for review see Ref. 183). Suppression of food intake by intraintestinal infusions of fats is mediated by CCK-1 receptors (246). Thus diminished sensitivity to fatty acids in animals adapted to high fat may be CCK dependent. Indeed, several studies have shown that rats (45, 48, 189, 215) (Fig. 3A) and mice (156) maintained on HF diets are also less sensitive to the suppression of food intake by exogenous CCK compared with rats maintained on

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**Fig. 3.** CCK-induced reduction of food intake (A) and gastric emptying (B) in rats adapted to LF and HF diets. A: data shown are percent reduction of 30-min food intake following 17-h food deprivation. CCK caused significantly greater reduction of intake at 0.5 and 0.25 μg/kg dose in LF- than in HF-adapted rats. B: During 10-min emptying, CCK inhibited gastric emptying of a 5-ml saline load in LF- and HF-adapted rats. Inhibition of emptying was significantly reduced in rats maintained on HF diet after CCK administration. *P < 0.05. [Adapted from Covasa M and Ritter RC (46, 48).]
HF Diet Alters Gastric Responses to CCK

Under normal feeding conditions, CCK functions to inhibit gastric emptying via CCK-1R-mediated control of pyloric contraction (185, 203). Similar to CCK-induced satiation, gastric emptying rate in response to CCK can be modulated via dietary manipulation. For example, administration of a range of CCK doses significantly inhibits gastric emptying less in HF-than LF-maintained rats (46) (Fig. 3B). In addition to maintenance on an HF diet, chronic adaptation to a high-protein diet has been reported to result in significant acceleration of gastric emptying of a protein meal (196). It is likely that increased gastric emptying in rats fed high-protein diet is mediated by CCK because devazepide, a CCK-1R antagonist, prevents accelerated gastric emptying following a meal (235). Thus chronic exposure to exogenous CCK or adaptation to high-protein of HF diets might alter gastric-emptying response to CCK and thereby attenuate CCK-induced reduction of food intake. On the other hand, it is also possible that reduced sensitivity to the satiation effects of CCK and the gastric-emptying effects of CCK are signs of reduced sensitivity in a shared neural control system. On the basis of the observation that intralipid-induced stimulatory effects on pyloric pressure in lean men are attenuated following a hypercaloric HF diet (25) and that CCK postprandial concentrations are increased (67), it is conceivable that the antropyloroduodenal responses to CCK may also be altered. Despite this, in one report, Little et al. (122) found that exposure to HF diet resulted in no change of gastric motility measures in response to an intravenous infusion of CCK. However, only one dose of CCK was tested during a continuous CCK infusion, the diets used were hypercaloric, and no control infusion was used. Therefore, a systematic examination using a range of doses and control conditions is necessary to establish differential responses in gut motility in response to CCK in humans consuming an HF diet.

HF Diet Alters Neuronal Responses to CCK

CCK reduces food intake by acting on vagal sensory neurons (148, 191, 202, 204). Surgical (179, 200) as well as chemical (184, 204) destruction of vagal sensory fibers abolishes CCK-induced reduction of food intake. Rats maintained on HF diet exhibit reduced hindbrain and enteric neuronal Fos-Li in addition to the attenuated inhibition of food intake and gastric emptying induced by exogenous CCK administration (43). The mechanisms by which an HF diet reduces sensitivity to CCK are not fully known. One explanation could be that HF diet reduces sensitivity or responsiveness of CCK-sensitive neurons themselves. It is well known that vagal sensory neurons express CCK-1Rs that mediate reduction of food intake and Fos expression in the NTS following CCK (92, 151, 152). Therefore, HF diet consumption could facilitate depolarization of sensory terminals; however, the exact location at which alterations in neuronal responses occur (enteroendocrine cells, vagal afferents, hindbrain neurons) needs to be identified.

Binding studies revealed the presence of functional CCK-1R in the vagus nerve (250) with a large population of nodose ganglia expressing high levels of CCK-1R mRNA (30). Differences in vagal CCK-1R may account for differential responses to CCK in animals maintained on an HF diet. In the obese Zucker rat, for example, the resistance to CCK and its effects on pancreatic secretion have been attributed, in part, to differences in peripheral CCK-1R binding (141, 157). However, in the nodose, Broberger et al. (30) using in situ hybridization reported no detectable variations in CCK-1R mRNA expression in regular Sprague-Dawley rats maintained 14 days on HF diet. On the other hand, Nefti et al. (156) found a downregulation of CCK-1R expression in mice fed HF diets for 15 days as measured by RT-PCR. The conflicting results of the two studies have not been addressed, and it remains to be determined whether decreased number of binding sites at the neuronal membrane surface is associated with changes in vagal sensitivity.

CCK-induced desensitization has also been demonstrated in several in vitro models (175). Thus, because fat is a potent CCK secretagog, it may be that modifications at the level of CCK-1R play an important physiological role (195). This is supported by evidence that continuous CCK infusion leads to downregulation of the receptor gene expression in rat pancreatic acinar cells (161) as well as in the central branch of the rat hypothalamo-pituitary-adrenal axis (131).

Altered Satiation Signals by Dietary Fats: Possible Mechanisms

In addition to reduced vagal and enteric neuronal sensitivity, ingestion of dietary fat is also associated with an increase in postprandial plasma CCK in rats (195, 205) and humans (68). Thus chronic administration of exogenous CCK or continuous elevation of circulating CCK may contribute to CCK desensitization. Indeed, sustained elevation of CCK either by diet or infusion of CCK via minipumps resulted in reduced sensitivity to exogenous CCK (45). It is known that gut-derived peptides, such as CCK and glucagon-like peptide (GLP)-1, act through G protein-coupled receptors, and chronic agonism of G protein-coupled receptors can induce receptor desensitization and downregulation (for review see Ref. 214). This may explain the robust and consistent effects of some peptides on food intake and weight loss with intermittent pattern of delivery. The ability of prior CCK exposure to reduce responses to subsequent CCK administration is well documented for several model systems of CCK action, including enzyme secretion by pancreatic acini in vitro (1, 159). In addition, Goke et al. (84) reported that CCK-induced release of amylase was reduced in pancreatic acini from rats, in which plasma CCK concentra-
tions were elevated by feeding trypsin inhibitor, before the harvesting of pancreatic tissue.

In addition to the abnormalities in the binding of CCK to its receptors in genetically obese rats, there are also CCK neuronal changes associated with dietary-induced obesity (DIO). For example, the early signs of obesity in neonatal overfed weanling rats were associated with a significantly decreased number of CCK-positive neurons in the paraventricular hypothalamic nuclei (171). Studies of CCK-receptor function in pancreatic acini and Chinese hamster ovary cells (176) indicate that receptor internalization and phosphorylation are important mechanisms for CCK-induced desensitization in vitro. Therefore, it seems plausible that reduced sensitivity to CCK could be mediated either by altered receptor protein translation or increased sequestration of previously translated receptors. Downregulation of transduction cascades has also been associated with CCK-induced desensitization of pancreatic amylase secretion (165). Therefore, a change in postreceptor transduction is yet another potential mechanism for reduced vagal sensory response to CCK. The present data suggest that modifications at the level of the CCK-1 receptors plays an important physiological role in the adaptation of feeding behavior; however, the relationship between decreased sensitivity to CCK or nutrient infusion in animals adapted to an HF diet and the functional characteristic changes occurring in the peripheral CCK-1 receptors has not been elucidated.

With in vitro systems, CCK-induced desensitization occurs rapidly and is reversed within tens of minutes (1). When examining CCK sensitivity in vivo, we have shown that maintenance on HF diet results in loss of sensitivity to the feeding-suppressing effects of CCK 2 wk following adaptation. On the other hand, the reacquisition of sensitivity to CCK-induced satiation after rats were switched from HF to LF diet took approximately 3 wk to restore (212) (Fig. 4). Thus dietary fat has the capacity to induce quick behavioral changes in CCK sensitivity while its effects, once established, last longer. This largely corresponds with changes in the GI functions reported in humans consuming an HF diet. For example, increased intestinal transit after fat exposure was still present 4 wk after dietary fat exposure (212) (Fig. 4). Thus dietary fat has the capacity to induce quick behavioral changes in CCK sensitivity while its effects, once established, last longer. This largely corresponds with changes in the GI functions reported in humans consuming an HF diet. For example, increased intestinal transit after fat exposure was still present 4 wk after dietary fat exposure (212).

HF Diet Alters Sensitivity to Other GI Peptides

Peptide hormones produced from the proximal and distal GI tract interplay with CCK to control food intake. Some of these interactions are fully established utilizing a CCK-dependent pathway to decrease food intake. For example, apo A-IV, a hypothalamic and intestinal signal released in chylous lymph in response to the hydrolysis of lipoproteins, has been shown to reduce food intake via a CCK-1R-dependent mechanism (127). Specifically, both components of chylous lymph or apo A-IV activate vagal afferents, and CCK-1R blockade reduces this response (80, 81). Furthermore, CCK-1R antagonism attenuates apo A-IV-induced hindbrain Fos-Li in rats (126). Behaviorally, applications of subthreshold doses of both apo A-IV and CCK result in significant reductions in meal size lasting for up to 4 h (127). The finding that HF feeding decreases the release of apo A-IV from both peripheral and central tissues may provide a further mechanism by which CCK-induced satiation is reduced (124, 245).

Similar, but not yet fully established, is the interaction between CCK and bombesin (BBS) that may underlie reduced sensitivity to satiation on an HF diet. BBS is an amphibian analog of several mammalian peptides that are released from GI tract and localized in the central nervous system (61). BBS inhibits food intake independently of CCK as evidenced by the finding that BBS, but not CCK, reduces food intake following vagotomy (200, 201). Although BBS appears to utilize a nonvagal pathway unlike CCK, BBS stimulates CCK secretion (51, 105), and the CCK-1R antagonist, proglumide, partially blocks the effect of high doses of BBS on food intake (42). In addition to being less sensitive to CCK, rats maintained on an
HF diet have also been reported to be less sensitive to BBS-induced reduction of intake (48). Similarly, obese women are less sensitive to the satiating effects of BBS (118). This suggests that obese state is associated with reduced response to this peptide. However, whether decreased responsiveness to BBS has an influence on reduced sensitivity to CCK-induced satiation is less clear. Altered production of gut peptides in response to dietary manipulations and their effects are not limited to CCK. For example, plasma GLP-1 levels are significantly lower in mice maintained on an HF diet (3), and HF-fed obese mice have elevated concentrations of GLP-1 in both ileum and colon. A number of other downstream mediators of CCK-induced satiety may be altered by dietary intervention as well. For example, cells expressing the CCK-1R in the nodose ganglia also contain cocaine- and amphetamine-regulated transcript, which encodes anorexigenic peptides (29, 94).

Finally, the endogenous cannabinoid system and related acylethanol-amides, such as oleoylethanolamide (OEA), that are produced by the gut and are potent mediators of GI functions have been shown to affect eating and energy balance (69, 70, 173, 192). Feeding, or intestinal infusion of fats, but not glucose or amino acids, stimulates intestinal production of the lipid messenger, OEA (192). Consistent with this, OEA administration results in short-lasting suppression of food intake, an effect mediated by the lipid activated nuclear receptor peroxisome proliferator-activated receptor-α (69). OEA acts locally within the gut by prolonging the inter-meal interval (69, 70, 166) and inhibiting gastric emptying (8, 192). It is also involved in regulation of fatty acid absorption in the gut and enhances fatty acid uptake in enterocytes (244). Thus OEA is highly regulated by dietary exposure, especially fat. Indeed, increased levels in gastric OEA have been observed in HF-fed obese mice (8). However, prolonged exposure to an oleic acid-enriched diet resulted in decreased small intestinal OEA levels in rats (5). Whether OEA plays a role in diminished sensitivity to CCK or whether adaptation to dietary fat results in decreased sensitivity to OEA is not known. The findings so far suggest that OEA signaling mediates lipid-induced satiety, an effect independent of CCK (174).

Like OEA, the endocannabinoids, are present in the gut and are involved in the control of food intake and several GI functions including inhibition of gastric emptying and secretion and intestinal motility (10, 103). These actions seem to be modulated by peripheral peptides (34) and nutritional status (33). For example, CCK administration reduces food intake and decreases vagal afferent cannabinoid 1 (CB1) receptor expression (32, 33). In DIO, endocannabinoid signaling undergoes adaptive responses that have consequences on food intake and gastric emptying (57). As such, exogenous administration of these compounds inhibits gastric emptying, and blockade of the CB1 receptor results in accelerated emptying on either normal chow or an HF diet. Furthermore, because the gut endocannabinoid production is tightly regulated by the amount of fat absorbed, there is a transient yet substantial increase of expression of these peptides following 14 wk of HF diet adaptation with retained effectiveness of the compounds (57).

It is less clear, however, whether the effects of an HF diet on endocannabinoids in mice are attributable to the macronutrient content or caloric density of the diet, as the HF diets used in these studies were hypercaloric compared with normal chow. Furthermore, feeding HF diets in mice typically results in obesity, adding one more confounding piece to these results. Nevertheless, it is important to note that gut cannabinoids may represent another signaling molecule that is responsible for HF diet-induced changes in GI functions.

**Increased Orexigenic Peptides in Response to High Fat**

In addition to decreased responsiveness to satiation signals such as intestinal nutrients, exogenous CCK, and BBS, HF foods may also promote intake by increasing sensitivity to orexigenic peptides. The hypothalamic forebrain nuclei are heavily implicated in the control of both short- and long-term control of food intake and energy regulation. Neuropeptide Y (NPY) and agouti-related peptide are both potent orexins involved in hyperphagia and obesity (20, 207). In some models, overexpression of the peptides results in obesity, whereas knockout of genes encoding these peptides prevents subsequent obesity (19, 22). For example, rodents maintained on HF diets that display hyperphagia also have significantly increased expression of NPY in the hypothalamus (21, 39). The increase of orexigenic signals in the forebrain, however, is not limited to long-term adaptation to an HF diet. Brief access to an HF meal also significantly increases expression of centrally acting orexigenic peptides. Gayinskaya et al. (71) showed, in chow-fed rats, HF preloads stimulate greater food intake over 24 h than LF preloads, which is associated with increased levels of orexin and an upregulation of galanin expression in the hypothalamus. Together, these data suggest that potentiation of positive feedback involving orexigenic signals, in addition to decreased negative feedback from anorexigenic satiation signals, following HF feeding is responsible for the overconsumption of an HF diet.

**HF Diets Alter GI Microbial Population**

In addition to morphological, digestive, and physiological changes at the level of the GI tract following prolonged exposure to an HF diet, the trillions of bacteria residing in the GI tract, commonly referred to as the gut microbiota, undergo population shifts in response to diet (56, 91, 221). This change has been found to be independent of obesity, as knockout models resistant to obesity as well as obese-prone rodent models display similar gut microbial populations when fed an HF diet (56, 221). Specifically, feeding an HF diet results in noticeable shifts from a population dominated by *Bacteroides* to one being comprised mostly of *Firmicutes* and *Proteobacteria*. One metabolic characteristic of this new population is increased short-chain fatty acid synthesis, predominantly in the colon, which enhances energy harvest from the diet (218, 220). Furthermore, this shift in the microbial population is associated with deleterious metabolic effects, including increased body adiposity (218). Therefore, nutritional experience plays a major role in intestinal functions and can predispose or contribute to the development of obesity. Indeed, recent evidence has demonstrated a role for the gut microbiota in obesity. For example, germ-free mice are resistant to obesity, and, when populated with microbiota, they increase body fat content despite a decrease in food consumption (9). This landmark finding implicates the intestinal microbial flora in obesity. Consequently, the presence of an “obese microbiome” has been suggested. This was based on several findings: 1) the transfer of gut microbes from an obese animal to a germ-free animal,
devoid of an intact gut microbial environment, results in an obese phenotype (113); 2) specific microbial populations significantly differ between lean and obese (219); and 3) weight loss in obese individuals shifts microbial populations to a composition similar to that of lean subjects (155, 251). The intestinal microbiota is highly responsive to nutritional changes, and that exposure to diets rich in a particular nutrient, such as fat, results in microbial and functional alterations of the small intestine, including inflammation, which has been suggested as a possible triggering mechanism for overconsumption and weight gain (56). Studies examining mechanisms underlying these phenomena are in infancy and may include alterations in gut peptide-signaling pathways. For example, production of short-chain fatty acids by gut microbiota results in stimulation of peptide YY secretion (188). Thus future work cannot overlook the gut microbiota as an important factor regulating GI functions and energy balance, as well as the ability of the host organism to respond to diet-induced changes in intestinal microbiota populations.

Do Diminished Responses to Satiation Signals Affect Long-Term Energy Balance and Body Weight?

The participation of GI satiation signals in the control of food intake and body weight has been an area of intense study for the past three decades (243). Although CCK is clearly involved in the control of ingestion and individual meals, how these actions translate into roles for CCK in overall meal-to-meal regulation or energy balance has not been obvious. In a classical study, West and colleagues (232) administered CCK before each spontaneous meal in rats and found that it continued to decrease meal size (i.e., there was no loss of sensitivity to the satiating effect of CCK), but 24-h food intake was not reduced because the rats increased meal frequency to compensate for the CCK effect on meal size. On the other hand, G. P. Smith et al. (35, 199) presented evidence for an effect of CCK on body weight; he and his colleagues adapted rats to three scheduled meals/day and injected CCK intraperitoneally before each of these meals. Under these conditions CCK had a substantial effect on body weight in both Zucker and DIO rats. In humans, a study by Beglinger et al. (17) showed that intracutaneous infusion of insulin enhances the satiety response to CCK in rats. From a number of experiments have indicated that the actions of CCK in food intake may depend, in part, on leptin signaling (14, 60, 134) and that both insulin and leptin modulate the effects of CCK (64, 65). For example, in rats that have a nonsense leptin receptor mutation and become obese, Morton et al. (153) have shown that CCK is ineffective in reducing food intake. When leptin signaling is restored in the hypothalamic arcuate nucleus, one of the primary sites of the action of leptin, the satiating effect of CCK and its activating effect on neurons in the hindbrain are reestablished. Furthermore, a subthreshold dose of intraventricular leptin significantly increases the magnitude of feeding suppression produced by peripherally administered CCK (134). Similarly, simultaneous peripheral administration of both peptides at subthreshold doses significantly reduces food intake. Leptin/CCK combinations also result in elevated levels of c-Fos expression in the hypothalamic paraventricular nucleus and nucleus of the solitary tract, as well as long-term inhibitory feeding effects beyond those produced by either stimulus independently (14), which lead to greater decreases in body weight as well (134). More recently, it has been shown that addition of CCK to leptin/amylin combination therapy resulted in enhanced and persistent weight loss beyond that obtained with dual leptin/amylin therapy (217). Although the specific cellular and molecular mechanisms of these multintegrated neurohormonal therapeutic approaches are still being worked out, it is clear that they engage a complex neuronal network in the forebrain areas that process, as well as exert control on, meal-related inputs coming from the hindbrain areas.

Obesity and Reduced Satiation Signaling

Obesity is a phenotypic trait expressed by a variety of rodent strains, including rats and mice with spontaneous genetic

Fig. 5. Short-term (3 h) daily exposure to an HF, high-energy (HHF) test food after 4 h of food deprivation in rats maintained for a minimum of 3 wk on LF or HF diets. During testing, half of each group was fed the HHF test food (LF/HHF; HF/HHF), whereas the other half was fed the respective maintenance diet (LF/LF; HF/HF). HF/HHF consumed 11.4 more calories than LF/HHF (P < 0.005) and 28.6 more calories than HF/HF (P < 0.001). Data are expressed as cumulative means ± SE in grams, during 15 days of testing at 1, 2, and 3 h of diet exposure. [Adapted from Savastano DM and Covasa M (189)].
mutations and experimentally produced gene deletions. Remarkably, obesity is a pathology consisting of concomitant alterations in a surprising variety of disparate genes. A short and nonexhaustive list includes deletions or mutations of leptin, melanocortins, gastrin-releasing peptide, 5-hydroxytryptamine-2c, and CCK-1R genes (7, 16, 109, 160, 170, 213). The variety of mutant and transgenically modified alleles associated with obesity reflects the complexity and diversity of processes that can impinge on control of body energy balance and the number of points at which this balance can be disturbed.

Increased food intake occurs in virtually all genetically obese rodents independent of strain. In some cases, however, increased food intake seems to be necessary for the development of obesity (149), whereas in other strains obesity often develops when increased food intake is not permitted (23, 40). Therefore, some genetic obesity may be caused by hyperphagia, and in others, hyperphagia may reinforce or exacerbate the gain of excess fat. Although there has been considerable interest in the behavioral and physiological mechanisms that lead to the etiology of obesity, little attention has been paid to consequences or concomitants of obesity contributing to maintenance or exacerbation of the obese state.

Reduced sensitivity to satiation mechanisms in obese individuals has been suggested (237); however, few studies have been performed in this area. For example, plasma GLP-1 levels are reduced in obesity (224), which is reversed by weight loss (222). Dietary fat intake that is equicaloric to high-carbohydrate diets has been associated with body fat and weight status in children (107, 108, 136). Comparatively, rats with DIO eat more fat equicaloric to carbohydrate (93, 227); however, hyperphagia is not always necessary for weight gain under HF conditions (163, 164). In humans, a strong correlation exists between fat intake and development of obesity (108, 226). Dietary fat intake that is equicaloric to high-carbohydrate diets has been associated with body fat and weight status (222). In some cases, however, increased food intake seems to be necessary for the development of obesity (149), whereas in other strains obesity often develops when increased food intake is not permitted (23, 40). Therefore, some genetic obesity may be caused by hyperphagia, and in others, hyperphagia may reinforce or exacerbate the gain of excess fat. Although there has been considerable interest in the behavioral and physiological mechanisms that lead to the etiology of obesity, little attention has been paid to consequences or concomitants of obesity contributing to maintenance or exacerbation of the obese state.

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Disordered Satiation in Obese Models

Most obese subjects exhibit disruptions in their responses to a variety of satiation signals such as diminished reports of hunger (67, 68, 115) and decreased sensitivity to GI peptides (117) compared with lean controls (see Table 1). Reduced responsiveness to CCK has been observed in several models of obesity, including the hypothalamic lesionated rat (18), genetically obese Zucker fatty rat (138, 142), and ob/ob mouse (15), although different results have also been reported (no difference in CCK sensitivity between obese and wild-type mice (209) or increased sensitivity to CCK in obese mice (15)). Decreased sensitivity to CCK may, in part, underlie the increase in meal size displayed by these obese animals. In some of these models, the diminished response to CCK seems to be diet dependent. For example, the hypothalamic lesionated rat is normally responsive to CCK when maintained on a chow diet but fails to respond to CCK when maintained on an HF diet (18). The Zucker rat, a homozygote for the fa gene, is a model widely used for the study of obesity. It has several characteristics in common with human obesity such as hyperphagia, hypertriacylglycerolemia, and hyperinsulinemia. Also, obese Zucker rats are less responsive than lean rats to intraperitoneal and intracutaneous administration of CCK (137, 138), and CCK antagonists or antibodies can increase meal size in lean subjects or concomitants of obesity contributing to maintenance or exacerbation of the obese state.

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Reduced SENSITIVITY TO SATIATION SIGNALS

but not in obese rats (208). Additionally, CCK measurements in the paraventricular nucleus, ventromedial hypothalamus, and suprachiasmatic nucleus after CCK administration are increased in the obese Zucker (140). Moreover, postprandial increases in plasma CCK are drastically reduced in obese fa/fa rats (89). Thus the mechanisms for the physiological satiating effect of CCK appear to be defective in the obese Zucker rats. This CCK resistance attributable to a decrease in CCK-receptor binding capacity (157) might, in part, contribute to the development of obesity. However, the primary cause of the Zucker rat obesity is a genetic defect in the leptin signaling pathway. Because the actions of leptin are required for CCK-induced satiation (153), the impairment in hypothalamic leptin signaling is another major contributor to decreased responsiveness to CCK in these animals. Although Zucker obese rats are less sensitive to CCK and intragastric loads of fats, they appear to be equally sensitive to the satiety effects of similar doses of BBS (138). Thus the interaction between gut signals, the neuronal control systems, and identification of the conditions under which altered sensitivity to satiation signals occur in genetic and DIO phenotypes remains a challenge.

The potential participation of satiation deficits in contributing to obesity was highlighted with the demonstration that the OLETF rat, which does not express CCK-1R, overeats and becomes obese. We have hypothesized that the primary cause of hyperphagia in this model is an increased feeding motivation unchecked by inhibitory signals (47, 49, 53, 54, 90, 211). OLETF rats do not reduce their food intake in response to systemic administration of CCK or intestinal nutrients and show diminished feeding responses and neuronal activation induced by gastric distention (47, 53, 193). Additionally, the OLETF model is characterized by impaired central mechanisms controlling food intake. Specifically, dorsomedial hypothalamic NPY neurons are under a tonic inhibitory influence of neuronal, not hormonal, CCK, such that OLETF rats overexpress NPY in the dorsomedial hypothalamus (DMH) (22). Furthermore, knockdown of NPY expression in the DMH results in significantly reduced body weight and adiposity in the OLETF (20). Thus this defective signaling is thought to be another major contributing factor to the overeating and obesity of these animals. OLETF rats also are resistant to peripheral leptin (158). Because of the reported synergistic interaction between CCK and leptin on food intake and body weight, defects in CCK signaling could have long-term consequences for body weight control. Indeed, Merino et al. (144) showed that CCK decreases body weight by a mechanism partially dependent on central leptin pathways. Finally, OLETF rats also have deficits in satiation in response to intestinal infusion of some but not all nutrients (47, 193). Specifically, we have demonstrated that OLETF rats exhibit marked satiation deficits in response to intestinal infusions of carbohydrates, which do not stimulate CCK secretion (47). Hence, it may be that some satiation deficits in Zucker fatty rats and OLETF rats result from the sequela of obesity and not directly or entirely from reduced CCK receptor function.

Reduced Sensitivity to Satiation Signals: Cause or Consequence of the Obese State?

Many insights into the physiological and metabolic abnormalities that predispose humans to develop and sustain obesity have come from animal studies. Most studies have examined the role of metabolic changes in genetically obese animals in which obesity is already a preexisting condition. This, together with the possibility that genetically obese rats may express neural alterations secondary to their mutant phenotype or other compensatory mechanisms, limits the interpretation of dietary effects in these models. Contrary to genetically obese models, DIO models offer the possibility of assessing changes where animals can be studied both before and after the expression of obesity produced by feeding high-fat diets. Thus the dietary-obese rodent model more accurately represents environmentally induced obesity in the human population that is heterogeneous (4).

DIO and Dietary-Resistant Rats

DIO rats and their dietary-resistant (DR) counterparts are used to delineate the contributing factors to obesity induced by changes in diet. Work in DIO models has shown that hyperphagia accompanies the persistent obesity produced by long-term, HF feeding (59, 62, 181, 225). In addition to the deficits in hypothalamic signaling (24, 41, 102, 112), there is evidence of adaptation of intestinal functions in response to the development of DIO. For example, there are differences in small intestinal secretomotor functions between DIO and DR (101) rats, indicating both the plasticity and the long-term changes at the level of the enteric nervous system. Whether these changes are the result or the cause of the obese phenotype is under investigation. However, DIO rats have altered peripheral sensitivity to food stimuli (58, 110). In fact, we (210) and others (37) have recently shown that obese DIO rats are more sensitive to peripheral CCK than DR rats after maintenance on either HF diet or chow. This is in contrast with studies showing decreased sensitivity to CCK in HF diet-fed animals and other obese models and, thus, could be interpreted as inconsistent with the overall hypothesis of increased food consumption because of loss of sensitivity to peripheral satiation signals such as CCK following HF diet exposure. However, the DIO rats are characterized by deficits in the central satiety signaling cascades, including permanent disruptions in hypothalamic neural leptin projections (24) and orexigenic peptide expression that may override, and/or impinge upon, the gut anorexigenic signaling to influence intake. This, together with increased body weight and leptin levels, given the interaction between leptin and CCK on food intake and body weight, may account for the increased sensitivity to CCK in the DIO rat. Thus, although CCK resistance alone may not be responsible for the hyperphagia of DIO, alterations in other satiety signaling pathways may influence their sensitivity to CCK.

Similar to outbred rodent strains, the OM rat is another model used to examine mechanisms involved in diet-induced obesity. These animals have numerous differences in feeding behavior involving orexigenic and anorexigenic signals, as well as GI and central systems (13, 87, 125, 197, 233). The OM rat is hyperphagic and obese relative to 55B controls after introduction to an HF diet. Among the underlying causes of overconsumption, an increased stimulatory signal as well as decreased inhibitory signals have been reported (78, 79, 87). For example, Greenberg et al. (87) showed that, compared with 55B rats, the OM rats have an attenuated response to the satiating potency of intestinally infused fats consistent with an
altered is the sensitivity to satiation signals. This is likely due to the fact that obese individuals have a decreased sensitivity to gut hormones such as CCK-1R, which are involved in the regulation of food intake and energy balance. The obese phenotype is less clear, and the relationship between adaptation to HF diet, diminished responses to GI satiation signals, and obesity is under intense investigation. However, studies in humans are limited, and the reports using obese subjects have shown inconsistent results, with many confounding factors that prevent unequivocal interpretation of the effects of adaptation to fats on the development of obesity. In most cases, this largely stems from the inability to discern the effects of the diet from the obese condition. As such, many findings come from preloads or single meals, which limit the interpretation of the results to short-term changes.

Although the effects of exposure to fats on GI responses including satiation signals are well documented, the results are likely to differ because of numerous factors including the model employed (strain, genetic background), the maintenance diet (obesigenic vs. nonobesigenic, solid vs. liquid, nutrient composition, caloric content), the testing diet used, the duration of the adaptation period, the doses of the peptides employed, and the metabolic status of the animal (fasted vs. nonfasted) among others. Thus controlling for these factors, although challenging, is imperative to isolate the effects of each of these variables in the absence or presence of obesity. Although pair feeding could potentially alleviate some of these problems in models that exhibit hyperphagia, this also results in drastically altered orexigenic peptide expression. Furthermore, chronic exposure to dietary fat may increase preference for high-caloric meals driven by their orosensory effects and a reduced sensitivity to the postabsorptive feedback signals, or both. Therefore, how exposure to dietary fats changes chemosensory input both pre- and postigestively warrants greater investigation.

Finally, diet can profoundly affect the composition of the gut microbiota, and indirect evidence suggests that the intestinal microbiota modulates the release and activity of the gut peptides (154). Also, several bacterial strains have been shown to display molecular mimicry with leptin, insulin, ghrelin, and other hormones (63). Therefore, gut microbiota may, through

**Disordered Satiation in Obese Humans**

Although a growing number of reports indicate that obese subjects, including humans, exhibit disruptions in their responses to satiation signals, specific studies examining changes in satiation signals in obese individuals are limited. For example, obese humans reported feeling less hungry than lean controls (67, 68, 117), and they were less sensitive to infusion of GI peptides such as BBS (117, 118). Although the mechanisms are not immediately apparent, changes at the CCK-1R have been suggested. Genome-linkage studies, for example, have identified CCK-1R as a strong positional trait-specific gene in individuals with increased susceptibility to obesity (6). Genetic association analyses also showed that obese individuals carrying the CCK_H3 haplotype have an increased risk of eating large portion sizes (55). Therefore, increased fat consumption, coupled with an individual’s genetic predisposition to developing obesity, may play a significant role in overeating and weight gain. Similarly, BBS receptor binding may be decreased in obese women, and it is possible that obese subjects are less sensitive to other GI peptides. The obese mouse also has a decreased sensitivity to CCK- and BBS-induced satiation (139). This decreased responsiveness occurs at a very early age and is not likely a consequence of obesity. Rather, decreased satiety may lead to increased meal size and contribute to hyperphagia and development of obesity. Likewise, it is possible that, in human obesity, decreased sensitivity to satiating effects of GI peptides occurs at a very early age and contributes to the development of obesity later in life.

Studies examining physiological changes in obese subjects such as gastric emptying have shown contradictory results (97, 100, 129, 216, 237, 249) with no systematic gastric emptying abnormality reported (168). Wright et al. (242) found that obese people emptied the solid component of a mixed meal more rapidly than a group of nonobese subjects, whereas the emptying of the liquid component was similar between groups. Horowitz et al. (96) observed a delay in emptying of the solid food, but Verdich et al. (223) showed that overall emptying rate did not differ between obese and lean subjects. However, the percentage of gastric emptying during the initial 30 min for a solid meal appeared to be increased in obese males. Fasting and postprandial plasma CCK levels in obese subjects are not different from normal-weight subjects (119). More recent studies, however, have found that both moderately and morbidly obese women have significant lower fasting plasma CCK concentrations and exhibit a blunted postprandial CCK response (12, 252). After consumption of a fatty meal, plasma CCK concentrations in obese subjects also remain significantly elevated compared with lean individuals (68). Furthermore, in obese subjects, exogenous CCK stimulated the pancreatic secretion of trypsin, amylase, and lipase, the emptying of bile acids, and the release of gastrin, at only half that of normal weight controls (239). Thus, despite early evidence suggesting similar levels of circulating CCK in obese and normal individuals, it appears that obese subjects have decreased sensitivity to CCK and decreased meal-stimulated release of the peptide.

**Perspectives and Significance**

Diet has a major impact at various anatomical and functional levels of the gut-brain axis, resulting in complex changes that affect energy consumption and regulation of body weight. The composition of the intestinal luminal content varies considerably with diet. The intestinal epithelium senses and responds to these significant changes and regulates its functions accordingly. Digestive functions adapt to accommodate variations in the macronutrient composition of a diet, and the capacity of the GI tract to digest and assimilate fats increases in response to maintenance on HF diet (11, 198, 205). Chronic exposure to HF diets also leads to changes in neuropeptides involved in food intake and energy regulation. For example, fat feeding leads to upregulation of hunger peptides (NPY, orexins, and agouti-related peptides) (99, 241), resulting in increased hunger for fat foods, whereas some satiety signals are downregulated, thus lowering the satiety response to an HF meal (48, 99).

There is ample evidence demonstrating that several gut hormones undergo changes in the obese. Whether this is a cause or a consequence of the development or persistence of the obese phenotype is less clear. The relationship between adaptation to HF diet, diminished responses to GI satiation signals, and obesity is under intense investigation. However, studies in humans are limited, and the reports using obese subjects have shown inconsistent results, with many confounding factors that prevent unequivocal interpretation of the effects of adaptation to fats on the development of obesity. In most cases, this largely stems from the inability to discern the effects of the diet from the obese condition. As such, many findings come from preloads or single meals, which limit the interpretation of the results to short-term changes.

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dietary manipulations, be used to change the gastric milieu in the interest of controlling intake and weight gain. In summary, understanding the role of fat intake in adaptation and plasticity of systems involved in the control of food intake and regulation of body weight is crucial in identifying potential physiological and pharmacological avenues to prevent or treat DIO.

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DISCLOSURES

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