# Modulation by high-fat diets of gastrointestinal function and hormones associated with the regulation of energy intake: implications for the pathophysiology of obesity[1−3]

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## ABSTRACT

The presence of fat in the small intestine slows gastric emptying, stimulates the release of many gastrointestinal hormones, and suppresses appetite and energy intake as a result of the digestion of fats into free fatty acids; the effects of free fatty acids are, in turn, dependent on their chain length. Given these effects of fat, it is paradoxical that high dietary fat intakes have been linked to increased energy intake and body weight and are considered to play a significant role in the pathogenesis of obesity. However, increasing evidence indicates that a chronic increase in dietary fat is associated with an attenuation of the feedback signals arising from the small intestine induced by fat, with a consequent relative acceleration of gastric emptying, modulation of gastrointestinal hormone secretion, and attenuation of the suppression of energy intake. This review addresses the gastrointestinal factors involved in the regulation of appetite and energy intake, with a particular focus on *1*) the gastrointestinal mechanisms triggered by small intestinal fat that modulate energy intake, *2*) the potential role of a high dietary fat intake in the development of obesity, and *3*) implications for the prevention and management of obesity. *Am J Clin Nutr* 2007;86:531–41.

## INTRODUCTION

Obesity can, in the broadest sense, be considered to be the result of an energy intake that exceeds energy expenditure. Signals arising from the gastrointestinal tract play a fundamental role in the regulation of appetite and energy intake, and evidence indicates that the gastrointestinal and hormonal mechanisms involved in the suppression of appetite and energy intake are compromised in obesity (1, 2). Hence, obesity may, at least in part, reflect a decreased sensitivity to the gastrointestinal effects of nutrients, particularly in the face of excessive calorie intake. Studies in animals and, to a much more limited extent in humans, indicate that consumption of a high-fat diet has the capacity to modulate the gastrointestinal responses to ingested fat and, thereby, leads to impairments in appetite regulation that favor the development of obesity. A number of factors potentially involved in the regulation of energy intake, including gastric emptying (3, 4), intestinal transit (3, 5), gastropyloroduodenal motility (6), and the secretion and/or action of gastrointestinal

peptides, including ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) (7–10) are altered by a high-fat diet.

This review summarizes current knowledge about the gastrointestinal regulation of appetite and energy intake, with a particular focus on *1*) the mechanisms triggered by fat in the gut that modulate energy intake, *2*) the potential role of a high dietary fat intake in the pathogenesis of obesity, and *3*) implications for the pathophysiology and prevention and management of obesity.

## INTERACTION OF FAT WITH THE GUT: IMPLICATIONS FOR THE REGULATION OF ENERGY INTAKE

Although an increased dietary fat intake apparently contributes to overconsumption (11, 12), it is pertinent to recognize that fat has effects in the gastrointestinal tract that favor the suppression of appetite and energy intake. The inhibitory effects of oral fat on energy intake result from the modulation of gastrointestinal, rather than "systemic," factors, eg, when infused intravenously lipid has no effect on energy intake (13). In healthy subjects, small intestinal infusion of lipid has the capacity to potently slow gastric emptying (14); stimulate the release of a number of gastrointestinal hormones, including CCK, PYY, and GLP-1; suppress ghrelin (15–17); and reduce energy intake at a subsequent meal (18). Increasing evidence indicates that the digestive products of fat, free fatty acids, are primarily responsible for triggering the gastrointestinal effects of fat (16, 19).

### Effects of small intestinal fat on gastrointestinal function

The interaction of nutrients, particularly fat, with receptors in the small intestine results in inhibition of gastric emptying (20, 21), which serves to prolong gastric distension and regulate the

rate at which nutrients enter the small intestine. Relaxation of the proximal stomach (22, 23), a decrease in antral and duodenal contractility (24), and an increase in tonic and phasic pyloric pressures (25) underlie the slowing of gastric emptying. These effects of fat on gastric emptying and gastrointestinal motility appear to be responsible, at least in part, for the inhibition of appetite and energy intake (26, 27). For example, there is a close relation between *1*) hunger with gastric emptying, such that as gastric emptying progresses, hunger increases, presumably as a result of decreased gastric distension (28), and *2*) the perception of fullness and subsequent energy intake with the amount of a meal in the distal stomach (26, 29). Furthermore, both distension of the proximal stomach with a water-filled balloon to ≥400 mL in humans (30) and the stimulation of isolated pyloric pressures by electric stimulation in dogs (27) are associated with a reduction in energy intake.

The presence of fat in the small intestine also modulates the secretion of a number of gastrointestinal hormones, including CCK (31), GLP-1 (32), PYY (15, 16), and ghrelin (16, 33), all of which have been implicated in the regulation of gastrointestinal function (34–37) and energy intake (38–41). There is substantial disparity in both the nutrient stimuli and site of secretion of these hormones. CCK is secreted from the I cells of the proximal small intestine (ie, the duodenal and jejunal mucosa) and is released in particular by the digestion products of fat and protein (17, 31, 42, 43), but also by glucose (44). GLP-1 is secreted from L cells located primarily in the distal small intestinal mucosa, predominantly in response to fat (17) and carbohydrate (45). PYY is secreted from L cells of the ileum and large intestine, particularly in response to long-chain fatty acids (46). The secretion of PYY also occurs in response to neurohumoral signals originating from the proximal gut, including CCK (47–50). Ghrelin, an endogenous ligand of the growth hormone secretagogue receptor, is primarily synthesized by oxyntic cells of the fundic mucosa (51), and, in contrast with the other gastrointestinal peptides, is suppressed by nutrient ingestion (16, 33, 52) and by both exogenous (49) and endogenous (50) CCK. Exogenous administration of $PYY_{3-36}$ (53) has also been reported to suppress plasma ghrelin concentrations, although the doses used would need to be considered to be supraphysiological. Specific antagonists are not currently available to evaluate the effects of endogenous PYY on ghrelin in humans. In mice, exogenous administration of a pharmacologic dose of $PYY_{3-36}$ did not suppress ghrelin over the time frame in which it has anorexigenic effects. Furthermore, in PYY knockout mice, plasma ghrelin concentrations were not different from those in wild-type animals (54). Ghrelin is also suppressed by the intravenous infusion of glucose (55) and during hyperinsulinemia (56).

## Importance of fat digestion to the effects of fat on gastrointestinal function and energy intake

Recent studies indicate that the digestion of fat, and the consequent release of free fatty acids into the small intestine, is a prerequisite for the effects of fat on gastric emptying, gastropyloroduodenal motility, gastrointestinal hormone secretion, appetite, and energy intake (17, 19, 57–61). For example, administration of tetrahydrolipstatin, a lipase inhibitor which is the active ingredient of the anti-obesity drug, orlistat, with a mixed-nutrient meal accelerates gastric emptying of both the solid and lipid phases (60). Furthermore, tetrahydrolipstatin also markedly attenuates the effects of intraduodenal infusion of triacylglycerol

on proximal gastric relaxation (58); antropyloroduodenal motility (17); the secretion of CCK, GLP-1, pancreatic polypeptide (PP), and PYY; and the suppression of ghrelin (16, 17, 58). In healthy lean male subjects, the acute inhibitory effects of a high-fat preload (70% fat) (19) and intraduodenal triacylglycerol (17) on subsequent energy intake are also attenuated after administration of orlistat.

The effects of free fatty acids on gastrointestinal motor function, gut hormone release, and energy intake are, in turn, dependent on their acyl chain length (62–65). In pioneering studies reported in 1968, Hunt and Knox (63) showed that intragastric infusions of fatty acids with an acyl chain length of ≥12-carbon atoms inhibit gastric emptying in humans, whereas those with ≤10 carbon atoms are ineffective. Consistent with this, fatty acids with ≥12 carbon atoms have been shown to relax the proximal stomach and reduce the amplitude of antral contractions more than fatty acids with ≤10 carbon atoms (64). Moreover, in healthy subjects, intraduodenal administration of lauric acid (12 carbon atoms) has been shown to stimulate phasic pressure waves localized to the pylorus and basal pyloric pressure and to suppress antral and duodenal pressure waves much more than an isocaloric infusion of decanoic acid (10 carbon atoms) (62). Similarly, intraduodenal infusion of fatty acids with 12 carbon atoms stimulates CCK secretion much more than does the infusion of fatty acids with 10-carbon atoms (62, 64); stimulates plasma GLP-1, PP, and PYY; and suppresses ghrelin, whereas fatty acids with 10-carbon atoms appear to have no effect (33, 62).

Given the pivotal role of fatty acid chain length in mediating the effects of fat on gastrointestinal motility and gut hormone secretion, it is not surprising that the effects of free fatty acids on appetite and energy intake are also dependent on their acyl chain length. In rats, intraduodenal infusions of 12-carbon fatty acids or oleic acid (C18:1) suppress food intake, whereas fatty acids with ≤10 carbon atoms appear ineffective (65). In healthy male subjects, a 90-min intraduodenal infusion of C18:1 (≈288 kJ), but not of C8 (≈163 kJ), has been reported to suppress energy intake (57); however, because the infusions were not isocaloric, the data are difficult to interpret. Nevertheless, recent observations from our laboratory have confirmed a marked inhibitory effect of the intraduodenal infusion of 12-carbon fatty acids, when compared with an isocaloric infusion of 10-carbon fatty acids, on energy intake (62). Infusion of 12-carbon fatty acids (≈140 kJ) reduced perceptions of hunger and the desire to eat and suppressed energy intake at a subsequent meal by ≈2857 kJ, when compared with both a control and 10-carbon fatty acids (62).

The precise mechanisms by which carbon chain length mediates the gastrointestinal effects of fatty acids remain poorly defined; however, differences in their absorptive pathways are likely to be important. Fatty acids with a chain length of ≤11 carbon atoms are predominantly absorbed from the gut directly into the portal vein (66), whereas fatty acids with a chain length of ≥12 carbon atoms are predominantly reesterified and packaged into chylomicrons that pass through the lymph to the circulation (67). Chylomicron formation is essential to the actions of fatty acids with >12 carbon atoms. In rats, inhibition of chylomicron formation via use of the detergent Pluronic L-81 (BASF, Wyandotte, MI) has been shown to abolish the effects of lipid on gastric emptying (68), the release of CCK and energy intake (69), and the activation of vagal afferents (70).

## Effects of increasing the length of small intestine exposed to nutrients on gastric emptying, gut hormone release, and energy intake

The effects of nutrients on gastric emptying and gastrointestinal hormone secretion are also dependent on the length, and, possibly, the region, of small intestine exposed to nutrients. An initial study in dogs implanted with small-intestinal fistulae showed that glucose, when infused into the entire duodenum (ie, unrestricted), inhibits gastric emptying but has no effect when the infusion is confined to the proximal 5 cm of the duodenum (20). A subsequent study, also in dogs, established that although both the proximal and distal small intestine are capable of inhibiting gastric emptying, inhibition was achieved only when >15 cm of the small intestine was exposed to nutrients, and maximal inhibition was achieved after exposure of >150 cm, irrespective of the nutrient concentration and the region exposed (71). The inhibitory effect of fat (sodium oleate) on gastric emptying is also dependent on the length of small intestine exposed; however, with fat, feedback arising from the proximal small intestine may be more potent than that arising from the distal small intestine (72). When considered together, these observations indicate that "length-dependent" feedback signals arising from the small intestine are of particular importance in the regulation of gastric emptying, ie, because a greater length of small intestine is exposed to nutrients, a greater feedback inhibition of gastric emptying results.

Because the regulatory gut peptides have differing distributions along the small intestine, modulating the length of small intestine exposed to nutrient would also be expected to influence their secretion; this concept is supported by recent observations in humans (44). For example, when glucose was confined to a proximal 60-cm segment of the small intestine by an occluding balloon, plasma concentrations of ghrelin remained unchanged; in contrast with the situation in which glucose was allowed access to the small intestine distal to the balloon, when plasma concentrations of ghrelin were markedly suppressed (44). Furthermore, whereas in this study the magnitude of the stimulation of CCK and gastric inhibitory peptide was not affected, the secretion of GLP-1 was apparently dependent on nutrient contact with the distal small intestine (44). These observations have important implications for the regulation of appetite and energy intake, and, indeed, in animal studies the suppression of energy intake by small intestinal nutrients has been reported to be dependent on the length of small intestine exposed to the nutrient. For example, in rats, when lactose or oleate was confined to a 35-cm region of the jejunum, they failed to decrease energy intake; in contrast, when lactose or oleate was allowed access to the entire length of small intestine, potent suppression of energy intake was evident (73).

The above considerations may be of particular relevance to the efficacy of the Roux-en-Y gastric bypass, a procedure that both minimizes gastric capacity and shunts nutrients to the distal small intestine and is arguably the most successful treatment for obesity currently available. Weight loss after this procedure was originally attributed to the small gastric reservoir; however, recent studies suggest that its efficacy may relate predominantly to distal small intestinal effects. The finding that postprandial plasma concentrations of GLP-1 and PYY (**Figure 1**) increase after Roux-en-Y gastric bypass (74–76) is consistent with this

**Plasma PYY concentrations**
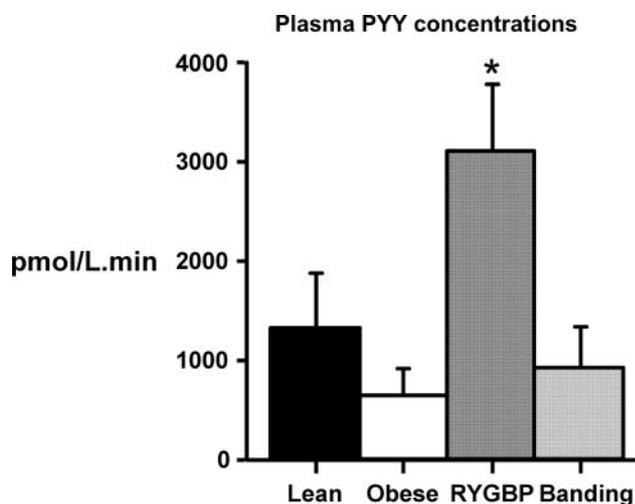


**FIGURE 1.** Mean (±SEM) integrated plasma peptide YY (PYY) concentrations in response to a 420-kcal test meal in normal-weight (lean) and obese subjects and in obese subjects 36 mo after Roux-en Y gastric bypass (RYGBP) or gastric banding surgery. After RYGBP, plasma PYY secretion was markedly enhanced. $n$ = 15, 12, 6, and 6 for the lean, obese, RYGBP, and gastric banding groups, respectively. *Significantly different from lean subjects, $P < 0.001$. Reproduced with permission (76).

concept, and the increased satiety reported by subjects after surgery (77), which leads to substantial weight loss, may well be the result of these hormonal changes. Clearly, further studies are indicated to establish whether such a relation exists. A number of studies have shown that plasma ghrelin is suppressed after Roux-en-Y gastric bypass (54, 74, 78, 79), although there are numerous reports of unchanged (80–82) or increased (83) plasma ghrelin concentrations. This decrease in plasma ghrelin concentrations has been postulated to account for the reduction in hunger and energy intake in obese patients after this procedure (76); however, significant weight loss can be observed in the absence of any change in ghrelin concentrations (81). The precise mechanism by which plasma ghrelin may be decreased after gastric bypass surgery is unclear. It has, however, been suggested that it relates to the bypass of the stomach so that few, or no, nutrients contact ghrelin bearing endocrine cells directly. It is, however, probable that the increased length of small intestine exposed to nutrients, particularly the distal small intestine, plays an important role, particularly given the evidence that exposure of the distal small intestine is required for ghrelin suppression by nutrients (44, 84). Nevertheless, a role for ghrelin in weight loss after gastric bypass surgery remains to be established.

## EVIDENCE FOR A ROLE OF A HIGH DIETARY FAT INTAKE IN THE DEVELOPMENT OF OVERWEIGHT AND OBESITY

Although the causes of obesity are heterogeneous, it is widely accepted that one of the salient environmental factors contributing to the current epidemic is the increased availability and overconsumption of high-fat, energy-dense foods. Epidemiologic studies have shown a direct relation between the incidence of overweight and obesity and dietary fat consumption (11, 85). For example, in those countries in which the incidence of obesity is rising rapidly, some 45% of the daily energy intake is provided by fat (11). Furthermore, there is evidence that obese subjects have

an increased preference for the consumption of fatty foods (86) and that the proportion of dietary fat is higher in obese, than in lean, individuals (87). The consumption of a diet high in fat has also consistently been shown to promote an increase in energy intake (12, 88), sometimes termed "high-fat diet hyperphagia." It has been purported that the increased availability of nutritionally unbalanced diets favors an increase in energy intake. This is consistent with the so-called "protein leverage hypothesis," which suggests that the intake of protein is tightly regulated and that fat and carbohydrate must be overconsumed to maintain protein consumption at a constant level during the consumption of high-fat, high-carbohydrate, low-protein diets (89). Animal studies have established that ad libitum access to a high-fat diet promotes hyperphagia and obesity and is associated with leptin and insulin resistance (90). Furthermore, when rats are exposed to an energy-restricted, high-fat diet, they maintain a body weight similar to that of pair-fed animals consuming a low-fat diet, but gain more adipose mass (90), which suggests that the fat content of the diet per se may influence fat deposition. Thus, there is substantial evidence indicating that the consumption of a high-fat diet promotes increased energy intake and body weight.

### Effects of a high-fat diet on appetite and energy intake and gastrointestinal function: implications for the pathogenesis of obesity

The precise mechanisms by which increased dietary fat intake promotes weight gain remain unclear. Consumption of a high-fat diet, however, has been shown in animal, and in a small number of human, studies to have the capacity to modify small intestinal morphology and pancreatic secretion (8) and attenuate the effects of fat on gastric emptying (3, 4, 91), gastrointestinal transit (5), antropyloroduodenal motility (6), the secretion, and the action of gastrointestinal peptides, including CCK, GLP-1, PYY, and ghrelin (7–9, 90, 92). These observations may be of fundamental relevance to the pathogenesis of obesity. There are, however, significant limitations associated with these studies. For example, the observed effects may relate to the very high level of fat supplementation ($\approx$45%) used in most studies in rats because rats typically consume a diet containing $\approx$5% of energy as fat. Furthermore, information relating to the effects of high-fat diets on gastrointestinal function and energy intake in humans are, in contrast with animal studies, much less conclusive, probably due, at least in part, to methodologic limitations incurred by the need to provide humans with normal food items. The following section will summarize what is known about the effects of exposure to a high-fat diet on gastrointestinal function and energy intake in both animals and humans. To place these observations in context, the regulation of gastrointestinal function and energy intake in obese subjects is then discussed briefly.

### Effects of a high-fat diet on small intestinal morphology

In rats, small intestinal morphology (93, 94) and pancreatic lipase secretion (8) are modified after a high-fat diet. For example, an increase in the amount of fat consumed from the diet (fat intake: 45% of daily energy) for 4 wk increased both small intestinal cell proliferation and the intestinal absorption of oleic acid (93–95). Furthermore, the secretion of pancreatic lipase, amylase, and proteases change in proportion to the dietary content of fat, carbohydrates, and protein, respectively (8, 96); in rats fed a high-fat diet containing ≥20% of the daily energy intake as
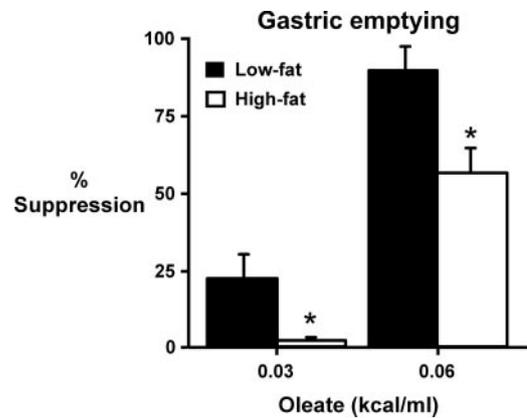


**FIGURE 2.** Mean (±SEM) percentage suppression of gastric emptying of a 5-mL saline load in response to intraduodenal infusion of sodium oleate at 0.03 or 0.06 kcal/mL for 20 min in rats exposed to either a high-fat (54% of energy as fat) or a low-fat (5% of energy as fat) diet for 2 wk each. Exposure to the high-fat diet attenuated the inhibitory effect of oleate on gastric emptying. $n = 6$. *Significantly different from the low-fat diet, $P < 0.05$. Reproduced with permission (4).

fat, the secretion of pancreatic lipase is increased (8, 96, 97). The hypertrophy of the intestinal mucosa, and increased capacity for fat digestion, would intuitively be expected to enhance the absorption of fat from the proximal small intestine and result in a decreased length of small intestinal exposure, which could, potentially, influence both gastrointestinal function and energy intake.

### Effects of a high-fat diet on gastrointestinal motor function

Studies in animals indicate that the gastrointestinal motor response to fat is attenuated after short-term (ie, 2–4 wk) diets containing high amounts of fat. For example, in rats, after exposure to a diet providing 54% of the total daily energy as fat for 2 wk, the inhibitory effect of a small intestinal infusion of oleate, but not of maltotriose, infusion on gastric emptying of 5 mL saline was attenuated, when compared with rats consuming an isocaloric diet providing 5% energy as fat (4) (**Figure 2**). Increased exposure of the small intestine to fat has also been shown to accelerate intestinal transit (5), so that in rats, the infusion of palm oil into the ileum for 3 h/d for 3 d/wk for 4 wk attenuated the lipid-induced slowing of small intestinal transit. This acceleration of fat transit was still evident 4 wk after the cessation of the oil infusions, which suggests that the adaptation of gastrointestinal function may occur more rapidly than the reversal of the changes; longer-term studies are indicated to evaluate this issue further.

In humans, similar effects on gastric emptying have been shown after exposure to a high-fat, high-energy diet. In healthy male subjects, the consumption of a high-fat diet (2340 kJ fat, 19.3 MJ energy/d) for 14 d resulted in acceleration of gastric emptying and mouth-to-cecum transit of a high-fat test meal when compared with a low-fat diet (105 kJ fat, 9.1 MJ energy/d) (3) (**Figure 3**). Ingestion of a high-fat diet has also been shown to modulate antropyloroduodenal motility (6). In healthy male subjects, exposure to a high-fat, high-energy diet (40% of energy from fat, 20.1 MJ/d) for 14 d attenuated the effects of an intraduodenal lipid infusion on antropyloroduodenal motility, when compared with a low-fat diet (11% of energy from fat, 11.2 MJ/d) (6).
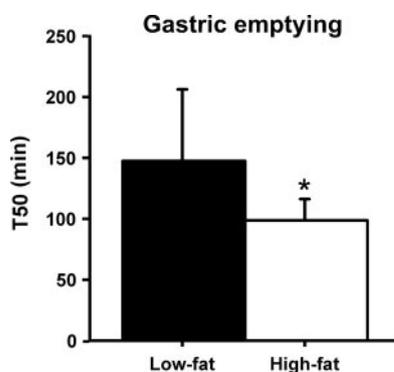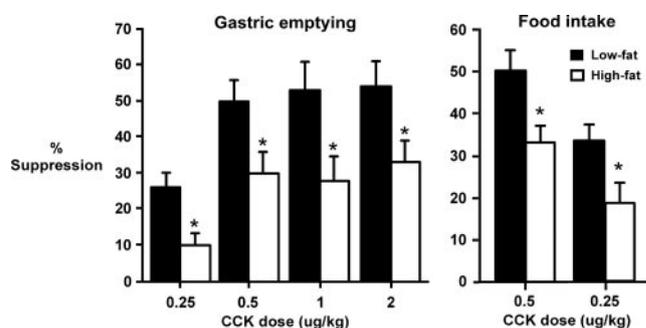
**FIGURE 3.** Mean (±SEM) time taken for 50% of a high-fat test meal to empty from the stomach (T50) in healthy lean male subjects in response to a high-fat (2340 kJ fat, 19.3 MJ energy/d) or a low-fat (105 kJ fat, 9.1 MJ energy/d) diet. Consumption of a high-fat diet accelerated gastric emptying of a high-fat meal compared with a low-fat diet. $n = 12$. *Significantly different from the low-fat diet, $P < 0.05$. Data adapted with permission (3).



**FIGURE 4.** Mean (±SEM) percentage suppression of gastric emptying of a 5-mL saline load in response to intraperitoneal infusion of 0.25, 0.5, 1, and 2 µg cholecystokinin (CCK)/kg (left panel) and energy intake in response to 0.25 and 0.5 µg CCK/kg (right panel) after exposure to a high-fat (34% of energy as fat) or a low-fat (5% of energy as fat) diet for 2 wk in rats. Exposure to a high-fat diet attenuated the inhibitory effect of exogenous CCK on gastric emptying and energy intake. $n = 6$ for gastric emptying; $n = 8$ for energy intake. *Significantly different from the low-fat diet, $P < 0.05$. Reproduced with permission from references 4 (left panel) and 106 (right panel).

Accordingly, it appears that increasing the fat or energy content of the diet accelerates gastric emptying. However, because of the marked difference in the total energy content of the diets, it is impossible to determine whether the observed changes in gastric emptying and small intestinal transit were related to the fat content of the diet per se or to the high energy intake. In another study, there was no significant difference in the gastric emptying of a high-fat test meal after exposure to a high-fat diet (55% of energy from fat) for 14 d (98); however, the high-fat diet was compared with a prediet condition in which both the fat and energy contents were uncontrolled (ie, the subjects' habitual diet contained 30–40% of energy as fat). Furthermore, in all studies, only small numbers of subjects have been included, the diets were of relatively short duration, and the consumption of the diets was, in general, not associated with a substantial change in body weight or adiposity; weight gain, if reported at all, was ≤ 2 kg. Therefore, studies using isocaloric low- and high-fat diets are required to determine the precise effect of increased dietary fat, as opposed to an increase in energy intake, on gastric emptying and gastrointestinal motor function in humans.

As with the studies that have evaluated the effects of high-fat diets on gastric emptying in humans, gastric emptying has been reported to be similar (99, 100), faster (101), and slower (102) in obese than in healthy lean humans. These discrepant observations may reflect differences in study designs (eg, the previous dietary intake of the subjects) and in inclusion criteria (eg, moderately compared with morbidly obese). It has been postulated that obese subjects may have a larger gastric capacity and, as a consequence, are able to consume larger meals without feeling full. However, reports of gastric volume in obesity are inconsistent and have been reported to be the same (103), and larger (30), in obese than in normal-weight subjects. Future studies investigating the effects of obesity on gastric emptying and motility should take into account the dietary history of the subjects.

### Effects of a high-fat diet on the secretion of and sensitivity to gastrointestinal hormones

The release of CCK, GLP-1, PYY, and ghrelin has been reported to be modulated after a high-fat diet (8, 9, 104, 105). By definition, changes in the secretion of, and sensitivity to, these

hormones have important implications for the regulation of gastrointestinal function and energy intake.

#### Cholecystokinin

A number of studies indicate that both the secretion of, and sensitivity to the actions of, CCK are modulated by a high-fat diet. For example, in rats, exposure to a high-fat diet (20% of energy as fat) for 14 d increased the CCK response to an intraduodenal triacylglycerol infusion by ≈1.7-fold (8). In rats fed a high-fat diet, the sensitivity to exogenous CCK also appears to be attenuated. For example, the inhibitory effects of an intraperitoneal injection of CCK-8 on gastric emptying (4) and food intake (106, 107) were reduced after exposure to a high-fat diet (34% or 54% of energy as fat) for 2 wk when compared with exposure to an isocaloric low-fat diet (5% of energy as fat) (**Figure 4**), in the absence of any change in body weight or adiposity. This suggests that chronically elevated plasma CCK concentrations, induced by an increased consumption of dietary fat, mediate the reduction in sensitivity to the inhibitory effects of CCK on food intake. There is, however, inconsistency in the available information. For example, the suppressive effect of intraperitoneally infused CCK-8 on energy intake has been reported to be maintained after consumption of a 34%-fat diet for 2 wk in rats (108). In rats that consumed a 60%-fat diet for 2 wk, the sensitivity to the satiating effects of exogenous CCK-8 has been reported to increase, rather than decrease, compared with rats maintained on a low-fat diet (108). The reasons for the discrepant observations are uncertain; however, it should be noted that the rats that consumed the 60%-fat diet gained more weight and adipose mass than did rats that consumed the 5%-fat or 34%-fat diets; it is, accordingly, possible that the effects of CCK on gastrointestinal function and energy intake are dependent on body weight.

In humans, although elevated postprandial CCK concentrations have been reported after exposure to a high-fat diet when compared with a prediet condition (7), the CCK response to intraduodenal infusion of lipid (2.8 kcal/min), which bypasses the influence of gastric emptying, was not affected by exposure to a high-fat diet (6) (**Figure 5**). It is likely, therefore, that the
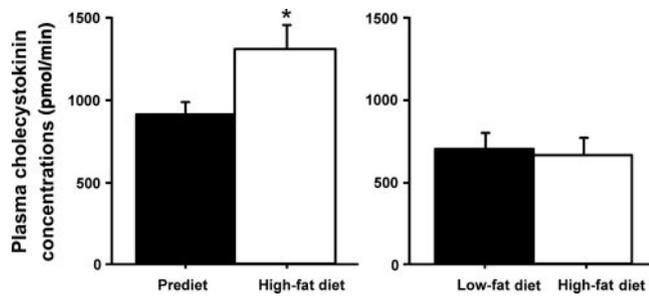
**FIGURE 5.** Mean (±SEM) plasma cholecystokinin (CCK) concentrations in response to ingestion of a standardized breakfast (3480 kJ, 42 g fat) after exposure to a high-fat (58% of energy as fat) diet for 2 wk compared with a prediet condition (left panel). Plasma CCK responses to an intraduodenal lipid infusion (Intralipid, 2.8 kcal/min for 90 min) after exposure to a high-fat (40% of energy as fat) or a low-fat (10% of energy as fat) diet for 2 wk (right panel). After the high-fat diet, plasma CCK responses to orally ingested, but not intraduodenally administered, lipid increased. $n = 12$ for both panels. *Significantly different from the low-fat diet, $P < 0.01$. Data adapted from references 7 (left panel) and 6 (right panel).

increased postprandial plasma CCK response in humans observed after consumption of a high-fat diet (7) is primarily reflective of more rapid gastric emptying (3), ie, a greater amount of nutrients present in the small intestine to stimulate the localized secretion of CCK. There is indirect evidence that the sensitivity to the actions of CCK may be attenuated in humans. For example, in the study by Boyd et al (6), which showed that the antropyloroduodenal response to an intraduodenal lipid infusion is attenuated after exposure to a high-fat diet, the plasma CCK response to lipid was not modified. The effects of exogenous or endogenous CCK on gastrointestinal function and energy intake after exposure to a high-fat diet in humans have, hitherto, not been investigated.

A potential role for CCK in the etiology of obesity is supported by the observation that rats genetically lacking functional $CCK_1$ receptors are hyperphagic and rapidly develop obesity (109, 110). However, although genetically engineered mice lacking $CCK_1$ receptors are insensitive to the inhibitory actions of exogenous CCK on energy intake, they have normal body weight (111), which may reflect the substantial redundancy in the signals involved in the regulation of energy intake. It is uncertain whether CCK has a role in the pathogenesis of human obesity. In humans, polymorphisms in the promoter region of the gene for the $CCK_1$ receptor have been reported to be associated with a higher percentage of body fat (112) and, accordingly, may contribute to increased body weight. However, mutations of the $CCK_1$ gene are infrequent in humans (113, 114). In obese subjects, fasting plasma concentrations of CCK have been reported to be increased in some (2), but not in all (31), studies, and CCK secretion is higher in obese than in lean subjects after a high-fat meal, despite comparable rates of gastric emptying (2-h integrated CCK secretion: obese subjects, $540 \pm 66$ pmol/L·min; lean subjects, $337 \pm 51$ pmol/L·min; $P < 0.05$) (115). The acute satiating effect of intravenous CCK-8 in obese subjects does not, however, appear to differ from that observed in healthy lean subjects (116, 117). Thus, CCK does not appear to play a major role in the pathophysiology of obesity in humans.

### Glucagon-like peptide 1

Limited information is available about the effect of a high-fat diet on plasma GLP-1. In a study in dogs that had increased their

body weight and adipose tissue mass after being provided with a hypercaloric, high-fat diet (≈40% energy from fat) for 12 wk, plasma GLP-1 concentrations were ≈2.5 times those of dogs fed a control low-fat diet in the fasting state and were 3.4-fold those of dogs fed a control low-fat diet in the postprandial state (104). No studies have evaluated the effects of exogenous GLP-1 on appetite and energy intake and gastrointestinal function after exposure to a high-fat diet; hence, it is unknown whether sensitivity to GLP-1 is attenuated, as appears to be the case with CCK.

In humans, the secretion of GLP-1 in response to an intraduodenal lipid infusion does not appear to be affected by a high-fat diet, when compared with a low-fat, low-energy, diet (6). It has not been determined whether exposure to a high-fat diet modulates the actions of exogenous or endogenous GLP-1 on gastrointestinal function or energy intake.

Animal studies suggest that GLP-1 does not play a major role in the regulation of body weight, because GLP-1 receptor knockout mice have a normal body weight (118). Lower plasma GLP-1 concentrations in obese than in lean subjects after oral carbohydrate intakes, but not after fat intakes (119, 120), have been reported. In contrast, fasting concentrations have been reported to be the same, and there were no differences in plasma GLP-1 concentrations in response to intraduodenal administration of fat and carbohydrate between healthy lean and obese subjects (121); hence, changes in gastric emptying may well account for the differences in GLP-1 secretion observed after meals. The inhibitory effects of intravenous GLP-1 on gastric emptying (122) and appetite and energy intake (122, 123) also do not appear to differ in obese subjects.

### Peptide YY

Although the secretion of PYY is modulated by a high-fat diet, PYY appears to maintain its inhibitory effect on energy intake. For example, in mice who had become obese in response to a high-fat diet (60% of energy as fat) for 16 wk, plasma concentrations of PYY were lower in both the fasting and postprandial states than in rats maintained on a low-fat diet (2.6% of energy as fat) (105). However, in wild-type mice, exposure to a high-fat diet (45% of energy as fat) did not attenuate the inhibitory effects of an intraperitoneal injection of $PYY_{3-36}$ on food intake (124). Furthermore, in obese mice fed a very high-fat diet (58% of energy as fat), chronic infusion of $PYY_{3-36}$ for a period of 7 d resulted in a sustained reduction in energy intake and body weight, which were associated with an increase in fat metabolism (10).

No studies have evaluated the effects of a high-fat diet on PYY secretion or the effects of exogenous $PYY_{3-36}$ on gastrointestinal function and energy intake in humans. Both fasting and postprandial plasma PYY concentrations have been reported to be lower in obese than in lean (fasting, obese: $10.2 \pm 0.7$ pmol/L; lean: $16.9 \pm 0.8$ pmol/L) subjects (53). There is also evidence that, for a given oral caloric load, plasma PYY is lower in obese than in lean subjects (105). In contrast, responsiveness to the anorectic effects of exogenous $PYY_{3-36}$ appears to be maintained in obesity (53).

### Ghrelin

The secretion of ghrelin has been reported to be modulated by the ingestion of a high-fat diet. In Long-Evans rats, who gained weight when fed a hypercaloric, very-high-fat diet (70% of energy as fat) for 14 wk, fasting plasma ghrelin concentrations

decreased by ≈30% when compared with rats fed a control (chow) diet (125). Likewise, in Sprague-Dawley rats exposed to a high-fat diet (48% of energy as fat) for 30 d, ghrelin messenger RNA concentrations and ghrelin secretion were reduced (9). The suppression of ghrelin by a high-fat diet may reflect an increased substrate-(fat-)induced inhibition of ghrelin secretion. This reduction in plasma ghrelin may represent an appropriate response to the increased calorie intake associated with high-fat diet consumption and serve to reduce the drive for further intake. The mechanisms by which ghrelin suppression occurs after exposure to a high-fat diet is unclear; however, as discussed, ghrelin is suppressed by hyperglycemia (55) and hyperinsulinemia (56), 2 common features of increased body weight associated with obesity. No studies have, hitherto, evaluated the response to exogenous ghrelin after exposure to a high-fat diet.

In humans, plasma ghrelin concentrations have been reported to be decreased after exposure to a high-fat diet, although the observations are inconsistent (126, 127). Healthy males ingesting a high-fat, cafeteria-style diet ad libitum for a period of 16 wk experienced no changes in fasting plasma ghrelin concentrations compared with a high-protein or high-carbohydrate diet (126). Another study reported that after supplementation of the habitual diet with high-fat products for 3 wk, the suppression of plasma ghrelin after an oral fat load was greater than at baseline, despite a mean increase in body weight of only 3% (127).

Ghrelin knockout mice do not have a higher body weight or energy intake than do wild-type controls (128), which argues against a role for ghrelin in the pathophysiology of obesity. Plasma ghrelin concentrations have been shown to be inversely related to body mass index (1, 55), whereas fasting ghrelin concentrations are reduced in obese individuals (1). This may relate, as suggested by animal studies, to an increase in the suppression of ghrelin as a result of an increase in caloric intake. The meal-induced suppression of ghrelin is also less in obese subjects (129).

### Effects of a high-fat diet on appetite and energy intake

In rats fed ad libitum with either an isocaloric (2.3 kcal/mL) high-fat (60% of energy as fat) or high-carbohydrate (76% of energy as carbohydrate) liquid diet for 16 d, daily energy intake is substantially greater with the high-fat (106 kcal/d) than with the high-carbohydrate (97.2 kcal/d) diet (130). It has been suggested that the increased energy intake associated with high-fat diets reflects increased palatability; however, it appears that comparable effects of fat are apparent after direct intragastric and small intestinal administration of nutrients, which bypasses any orosensory and hedonic inputs. For example, in rats fitted with intragastric pumps that allowed self-infusion of either a high-fat or a high-carbohydrate liquid diet, rats receiving the high-fat liquid infused a greater amount of calories than did those receiving the high-carbohydrate liquid (131).

Studies in humans have shown that intake of a high-fat diet increases energy intake. For example, in healthy females, covert manipulation of the dietary fat content resulted in a 15.4% increase in total daily energy intake during the consumption of a high-fat diet (45–50% of energy as fat) when compared with the consumption of a medium-fat diet (30–35% of energy as fat) for 2 wk, and this was associated with weight gain (12) (**Figure 6**). Furthermore, this increase in energy intake occurred in the absence of any change in perceptions of the palatability of the diets. Similarly, in healthy male subjects, Tremblay et al (88) reported
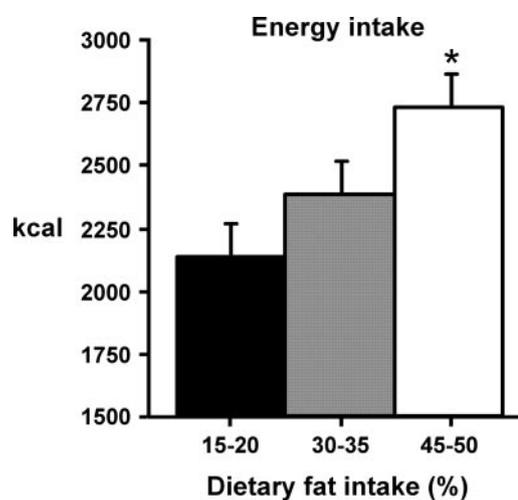


**FIGURE 6.** Mean (±SEM) daily energy intake over a 14-d period in response to covert manipulation of the fat content of the diet in healthy female subjects. Increasing the fat content of the diet resulted in an increase in the average daily energy intake. $n = 24$. *Significantly different from the 15–20%-fat diet and the 30–35%-fat diet, $P < 0.0001$. Reproduced with permission (12).

that a marked increase in acute energy intake occurred after a very short-term (2 d) increase in the fat content of the diet. French et al (7) reported that appetite perceptions were modified after exposure to a high-fat diet (58% of energy as fat) for a 2 wk, with hunger increasing and fullness decreasing, in healthy male subjects who had gained ≈2 kg of weight. They also reported a modest increase in energy intake from a preselected meal, and an increase in average daily energy intake, as measured by food diaries, was maintained over the 2-wk dietary intervention (7).

A positive relation between increased BMI with decreased fullness and a delayed onset of satiety has been reported (132). Furthermore, in obese subjects the satiating efficiency of oral nutrients is decreased (133, 134). Hence, obese subjects may well have to increase their intake to gain the same satisfaction from their intake as do lean subjects. In contrast, no differences in the effects of intraduodenal nutrients on energy intake were evident in a small cohort of obese and healthy lean subjects (135). This suggests that differences in gastrointestinal hormone secretion, perhaps resulting from changes in the rate of delivery of nutrients to the small intestine, may play an important role in the deregulation of energy intake in obesity. Future studies should, accordingly, determine the influence of previous dietary and nutrient intakes on energy intake in obese subjects.

The evidence summarized above provides a persuasive rationale for the hypothesis that consumption of a high-fat diet promotes increased energy intake and the development of obesity. In general, animal studies suggest that the consumption of a high-fat diet attenuates the effects of fat on gastrointestinal motor function and gastrointestinal hormone secretion, which favor a reduction in energy intake, particularly when the animal becomes obese. This adaptation of gastrointestinal function may potentially attenuate the signals involved in the feedback inhibition of appetite and energy intake, which suggests that changes in the sensitivity to intestinal fat are likely to contribute to the increased energy intake and obesity manifested by high-fat diets. In humans, gastric emptying of fat appears to be accelerated, and the secretion of gastrointestinal hormones modulated, by a high fat

intake; however, no studies have hitherto determined whether sensitivity to the actions of these hormones on gastrointestinal function and energy intake is attenuated.

The changes in gastrointestinal function in obesity would appear to promote increased energy intake and predispose to weight gain. Large controlled studies are indicated to determine whether these factors are, or are not, modulated in obesity and to determine to what extent any effects contribute to disturbances in energy intake. Although CCK and GLP-1 appear unlikely to play a major role in the pathogenesis of human obesity, studies using specific antagonists would be of interest. The attenuated secretion of PYY associated with obesity may lead to increased energy intake. These observations suggest that targeting the $PYY_{3-36}$ pathway may provide a potential therapeutic treatment for obesity. Impaired postprandial responses of ghrelin, ie, a failure to suppress ghrelin concentrations in response to energy intake may result in an attenuated suppression of hunger and consequently promote larger meal sizes and energy intakes in obese subjects. Future studies should evaluate the effects of interactions between different gastrointestinal hormones, because the studies discussed above indicate that the administration of these gut hormones alone is unlikely to be effective at reducing energy intake in the long term, and the effects of more modest differences in dietary fat intake in human studies also warrant investigation.

## CONCLUSIONS

This review has summarized current knowledge relating to the effects of fat in the gastrointestinal tract and the effect of both a high-fat diet and obesity on gastrointestinal function, appetite, and energy intake. Studies in animals have characterized numerous changes in gastrointestinal function, particularly in the secretion and signaling of gastrointestinal hormones in response to increased fat intakes, which may predispose to an increase in energy intake, and consequently, to weight gain and obesity. Currently, studies evaluating the effects of high-fat diets on gastrointestinal function and energy intake in humans are limited, and their interpretation made difficult, by methodologic issues. Thus, whether the observed changes in gastrointestinal function reflect an increase in the fat content of the diet per se, or an increase in carbohydrate and total energy intakes, remains uncertain. Hence, although the consumption of a high-fat diet appears to attenuate the effects of fat on gastrointestinal function and energy intake, and this may promote increased body weight, further studies are required to identify the mechanisms underlying the development of obesity, ie, well-controlled studies to determine gastrointestinal motor and hormonal function should be conducted under conditions in which the previous dietary nutrient exposure of an individual is taken into account and controlled for. It is likely that the signals arising from the distal small intestine, as evidenced by the impairment of PYY secretion, and the efficacy of Roux-en-Y gastric bypass, play an important role in the regulation of appetite and energy intake and are of pathogenic relevance to the development of obesity.

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