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Upper gastrointestinal sensitivity to meal-related signals in adult humans – relevance to appetite regulation and gut symptoms in health, obesity and functional dyspepsia

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ABSTRACT

Both the stomach and small intestine play important roles in sensing the arrival of a meal, and its physico-chemical characteristics, in the gastrointestinal lumen. The presence of a meal in the stomach provides a distension stimulus, and, as the meal empties into the small intestine, nutrients interact with small intestinal receptors, initiating the release of gut hormones, associated with feedback regulation of gastrointestinal functions, including gut motility, and signaling to the central nervous system, modulating eating behaviours, including energy intake. Lipid appears to have particularly potent effects, also in close interaction with, and modulating the effects of, gastric distension, and involving the action of gut hormones, particularly cholecystokinin (CCK). These findings have not only provided important, and novel, insights into how gastrointestinal signals interact to modulate subjective appetite perceptions, incl. fullness, but also laid the foundation for an increasing appreciation of the role of altered gastrointestinal sensitivities, eg. as a consequence of excess dietary intake in obesity, or underlying the induction of gastrointestinal symptoms in functional dyspepsia (a condition characterised by symptoms, including bloating, nausea and early fullness, amongst others, after meals, particularly those high in fat, in the absence of any structural or functional abnormalities in the gastrointestinal tract). This paper will review the effects of dietary nutrients, particularly lipid, on gastrointestinal function, and associated effects on appetite perceptions and energy intake, effects of interactions of gastrointestinal stimuli, as well as the role of altered gastrointestinal sensitivities (exaggerated, or reduced) in eating-related disorders, particularly obesity and functional dyspepsia.

Keywords: Food intake, dietary fat, cholecystokinin, peptide YY, glucagon-like peptide-1, humans, obesity, functional dyspepsia, gut symptoms, gastrointestinal sensitivity

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1. INTRODUCTION

As the first point of contact for food with the body, the upper gastrointestinal tract provides a critical source of information on the physical and chemical characteristics of a meal. Thus, the ingestion of a meal triggers a number of signals in the upper gastrointestinal lumen. These include distension of the stomach and interactions of dietary nutrients and their digestion products with receptors located on enteroendocrine cells in the small intestinal mucosa, associated with the release of gut hormones (25, 91, 116). These signals are then transmitted to the brain where they modulate hunger and fullness, and contribute to the regulation of eating, food choice and other behaviours, as well as feedback control of gastrointestinal functions (25).

As the meal is transferred gradually from the stomach into the small intestine, the signals from nutrients become increasingly more important. Experimental studies have established that when administered directly into the duodenal lumen, amongst the dietary macronutrients, lipid provides the most powerful signal to modulate gastrointestinal functions in healthy humans, including contractile events in the gastrointestinal wall and gut hormone release (3, 115, 121, 127). These effects of lipid are influenced by the fat droplet size (130) and require fat digestion (51, 94) and the release of fatty acids, particularly those with a chain length of ≥12 carbon atoms (58, 96). Moreover, it is increasingly apparent that the "sensing" of lipid in the small intestinal lumen, and the associated stimulation of these gastrointestinal functions, plays an important role for the suppression of subsequent energy intake (128).

There is evidence from studies in humans that gastrointestinal sensitivity to these stimuli can be altered in eating-related disorders, e.g. obesity and functional dyspepsia, associated with changes in appetite and energy intake, and the triggering of upper gut symptoms (71, 113,

119, 131). For example, obesity, on the one hand, appears to be associated with a reduced sensitivity to both oral and small intestinal lipid, and increased energy intake, which, however, can be reinstated, at least partially, by dietary restriction (129, 138). On the other hand, luminal sensitivity to both gastric distension and small intestinal lipid appear to be abnormally enhanced in patients with functional dyspepsia, triggering gastrointestinal symptoms, including nausea and bloating, and limiting their ability to finish normal-sized meals (9, 141).

This paper will review the effects of the two main stimuli arising directly from meal ingestion, gastric distension and duodenal nutrients, with a focus on lipid, and their interactions, on gastrointestinal function, and associated effects on appetite perceptions and energy intake. It will also consider the potential role of altered gastrointestinal sensitivities (exaggerated, or reduced) in eating-related disorders, specifically obesity and functional dyspepsia, exploring the hypothesis that the gastrointestinal responses to these stimuli can be disturbed, either desensitized (in obesity) or hypersensitive (in functional dyspepsia), associated with, or reinforcing, disordered eating. While it is recognized that a number of other population groups and disorders are also associated with alterations in the gastrointestinal responses to luminal stimuli (e.g. across the life-span, anorexia nervosa, acute care/trauma patients), their discussion is beyond the scope of this review.

2. SIGNALS ARISING FROM THE UPPER GASTROINTESTINAL TRACT IN RESPONSE TO MEAL INGESTION

During meal ingestion, the stomach is gradually filled, associated with gastric distension, and as gastric emptying progresses, nutrients enter the small intestinal lumen and interact with receptors located in the small intestinal mucosa (25). Both stimuli provide powerful signals,

and also interact, to modulate appetite, other gastrointestinal perceptions and symptoms, as well as subsequent energy intake.

2.1. Effects of gastric distension on appetite perceptions and energy intake

The mechanical distension of the stomach in response to a meal has long been implicated in the induction of fullness and regulation of acute meal intake (30, 43, 64, 100). In the process of food ingestion, the proximal stomach relaxes to accommodate the meal without a substantial rise in intragastric pressure (6). A gradual increase in wall tension and phasic pressures within the proximal stomach then leads to an ongoing transfer of gastric contents into the distal stomach, where it is ground into small particles by carefully coordinated phasic antral and pyloric contractions, appropriate for delivery into the small intestine (140). Thus, both proximal and distal gastric regions are distended by the meal, with the signals conveyed to the central nervous system by different populations of mechano-sensitive vagal and spinal afferents (67), and, therefore, may contribute to the induction of gastrointestinal perceptions and regulation of meal size.

The distension component of a meal can be replicated experimentally using flaccid, oversized (thus, infinitely compliant) bags, positioned in the stomach and connected to an electronic barostat, a distension device that allows standardized volumetric distension, while measuring resulting pressures, or vice versa (5, 50). Distension of the bag positioned in the proximal stomach with air has been shown to reduce hunger and induce a pressure-like fullness at a volume of ~440 ml, and, at higher volumes (~600 ml), a sensation of discomfort or pain, with these sensations subsiding as soon as the bag was deflated (49). Moreover, the threshold volume at which fullness was perceived was lower at a slower rate of distension (79), suggesting that different populations of gastric mechanoreceptors may be activated by

different rates of distension, and, thus, that the rate of meal ingestion may play an important role in the induction of fullness and, perhaps, meal termination. Distension of the stomach by means of filling a bag positioned in the proximal stomach with 500 ml water also induced fullness (100), and distension with water volumes of 400 - 800 ml reduced energy intake in a volume-dependent manner (64), while lower volumes of 200 or 300 ml were ineffective (64, 80), however, due to the weight of the water it is not clear which part of the stomach was distended. Pre-distension of the proximal stomach with air volumes of 400 - 800 ml has been reported not to affect subsequent food intake (106), however, the distension stimulus was removed prior to meal ingestion, thereby indicating that the effect of distension is short-lasting.

Experimental distension of the distal stomach (antrum) in humans remains a methodological challenge, because of the difficulty of maintaining an air-filled bag in the dependent part of the stomach. While this can be achieved more easily with a water-filled bag, it is more difficult to remove water quickly in case of nausea or other symptoms. The effects of distal gastric distension on appetite perceptions, or energy intake, have, therefore, been evaluated mainly indirectly in studies that have investigated the relationship between content of the antrum and appetite perceptions or subsequent energy intake following ingestion of a test-meal (74, 75, 139). For example, following ingestion of a 350-ml glucose drink, the perception of fullness was closely related to antral area (as a measure of antral content) in healthy subjects (74, 75). Moreover, energy intake after a 400-ml yogurt preload was inversely related to antral area in both healthy young and older subjects, so that a larger antral area was associated with a lower energy intake (139). One study, already mentioned above, which, in addition to pre-distension of the proximal stomach, also evaluated the effect of pre-distension of the antrum by inflating a bag with 300 ml air, found no effect on subsequent

food intake, however, the antral distension stimulus was removed prior to ingestion of the test meal (106), thus, as for the proximal stomach, the effect of antral distension appears to be short-lasting, and its presence a prerequisite for an effect on intake.

While these studies provide evidence that gastric distension, including both the proximal and distal stomach, plays a role in the induction of appetite-related gastrointestinal perceptions and the suppression of energy intake, it is also evident that its contribution is transient, since the effects disappear as the distension stimulus is removed, suggesting that the ongoing stimulation of gastric mechanoreceptors is necessary. In this context, it is also relevant to consider the contribution of gastric distension to the processes of "satiation" and/or "satiety", as proposed in the satiety cascade (14). Thus, "satiety" has been defined as the inhibition of hunger and further eating as a result of food consumption, measured as either the length of the inter-meal interval and/or the amount consumed at a subsequent meal. Satiety is, therefore, likely to be determined by intestinal and postabsorptive factors. In contrast, "satiation" refers to the process that controls meal size by terminating a period of eating, and is likely to be regulated primarily by factors that arise immediately during, or soon after, eating, such as orosensory and cognitive influences, gastric distension and the secretion of some gastrointestinal peptides. Thus, mechanical gastric distension primarily provides a signal for meal termination, or satiation.

2.2. Effects of dietary lipid on gastrointestinal functions, appetite perceptions and energy intake

In the process of gastric emptying, nutrients enter the small intestinal lumen where they interact with a large number of specialized receptors (42), and the contribution from gastric distension gradually diminishes. The nutrient-receptor interaction results in the activation of a

range of physiological processes, including the slowing of gastric emptying, through well-coordinated modulations of the contractile activity in the antropyloroduodenal region, and the release of gut hormones, associated with modifications in appetite and subsequent energy intake. While all three macronutrients influence these processes in a dose-related fashion (112, 115, 120), lipid appears to have the most potent effects (121, 127).

Direct administration of lipid into the duodenal lumen, thereby allowing investigation of the exclusive contribution of sensory inputs from this region, while excluding any potential influences from oral or gastric sensory inputs, suppresses contractile activity in the antrum and duodenum, and stimulates tonic and phasic pyloric pressures (115, 121) (**Figure 1**). These events, particularly pyloric pressures, underlie the slowing of gastric emptying (in the presence of a meal in the stomach) (68), thereby prolonging gastric distension. Small intestinal lipid is also a potent stimulus for the release of gut hormones, including cholecystokinin (CCK) from I cells located predominantly in the proximal small intestine, and glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), both from L cells predominant in the distal small intestine, while the release of ghrelin, secreted from X/A cells located in the proximal stomach and characterized by high circulating levels in the fasting state, is suppressed (86, 137, 144). Moreover, duodenal lipid infusion reduces hunger and subsequent energy intake (95, 115). Indeed, we have previously identified the magnitude of stimulation of both plasma CCK concentrations and pyloric pressures as independent determinants of energy intake in response to duodenal lipid (128). Thus, while it is currently not possible in humans to directly, and non-invasively, assess gastrointestinal lipid sensing, these physiological gastrointestinal functions can be used as indirect markers for gastrointestinal luminal sensitivity to nutrients, particularly lipid.

The effects of lipid on gastric emptying, upper gastrointestinal motility, gut hormone release, gastrointestinal perceptions, appetite and energy intake require digestion, or hydrolysis, of fat (16, 51, 52, 94, 111, 124). The speed and effectiveness of fat digestion is controlled primarily by the ability of lipase to bind to the surface of fat emulsion droplets, with the overall droplet surface increasing exponentially as droplet size decreases (4). Using experimental emulsions varying in their droplet sizes, it has been established that lipid droplet size also affects gut function, appetite and subsequent intake (73, 93, 130, 136). For example, gastric emptying is slower, pyloric stimulation greater, hunger reduced and fullness increased, stimulation of gut hormones, including CCK and PYY, enhanced and acute energy intake in response to the lipid emulsion reduced, as droplet size decreases. Further evidence for a key role for fat digestion for the effects of lipid on gut motor and hormone functions and energy intake comes from physiological studies using orlistat, an inhibitor of gastric and small intestinal lipases (16, 40, 51, 52, 56, 94, 111, 124). These studies have demonstrated that inhibition of fat digestion, and the associated release of fatty acids, by orlistat prevents fat-induced slowing of gastric emptying (111), stimulation of pyloric pressures (51), stimulation of the gut hormones, CCK, PYY and GLP-1, and suppression of ghrelin (51, 56, 94), as well as suppression of hunger and subsequent energy intake (51, 94).

Once released in the process of digestion, the gastrointestinal effects of fatty acids depend on their acyl chain length. Early studies revealed a fatty acid chain-length dependent effect on the slowing of gastric emptying in humans (72), so that fatty acids with 12 or more carbon atoms in their chain emptied from the stomach more slowly than fatty acids with 10 or fewer carbon atoms in their chain. Moreover, studies in rats found that small intestinal infusion of lauric acid (a C12-fatty acid), but not decanoic acid (C10) or octanoic acid (C8), reduced food intake following the infusion (101). A number of subsequent studies confirmed, and

extended, these findings in humans, demonstrating that lauric or oleic (C18:1), but not octanoic or decanoic, acids, potently stimulated the release of gut hormones, modulated upper gastrointestinal motor function, suppressed hunger and increased fullness and/or reduced energy intake from a test-meal provided immediately after administration of fatty acids (58, 59, 94, 96).

While knowledge of the receptor/sensing mechanisms involved in the mediation of the effects of fatty acids, and other nutrients, has rapidly evolved in the last decade, based on data from cell models and experimental animals (38, 42, 44, 45), clinical studies in humans remain scarce. In humans, the involvement of specific receptors in mediating the effects of lipid on gut function and appetite has been studied using specific receptor antagonists, particularly the CCK-A receptor antagonist, loxiglumide, or, subsequently, its (D−)enantiomer, dexloxiglumide (47, 78, 94), although these are no longer available for use in humans. Intravenous administration of loxiglumide diminished the effects of a lipid-containing, mixed-nutrient, duodenal infusion on antropyloroduodenal pressures (78), and the modulatory effects of intraduodenal lipid on appetite and gastrointestinal perceptions induced by gastric distension (47), and on subsequent energy intake (94). Moreover, a recent fMRI study has provided evidence that the transmission of information induced by the presence of fatty acids in the gastrointestinal lumen to the brain is mediated, at least in part, by CCK-A receptors, since the increase in activity in the brainstem and hypothalamus induced by the fatty acid, lauric acid, was abolished by dexloxiglumide (81). The involvement of GLP-1 receptors in the lipid-induced effects on gut function, energy intake and gut-brain signaling in humans remains to be established, although a role is likely, since, for example, the GLP-1 receptor antagonist, exendin(9-39)amide, abolishes the effect of intraduodenal glucose on pyloric

pressures in healthy humans (123). There are currently no receptor antagonists for other hormones, e.g. PYY, available for use in humans.

2.3. Interactions between gastric distension and small intestinal lipid

While both gastric distension and duodenal lipid infusion have distinct effects on the upper gut, appetite and energy intake, as discussed, it is well established that these two stimuli interact to potently modulate gastrointestinal perceptions and sensitivity (48, 49, 106). Experimental application of these stimuli in a standardized manner involves intubation of the study participants with custom-designed catheters, including a nasoduodenal catheter used for the infusion of nutrient or control solutions, and an orogastric catheter, with a thin-walled, flaccid bag attached to, and tightly wrapped around, its distal end, used to distend the stomach (**Figure 2**) (49, 106).

2.3.1. Effects on gastrointestinal perceptions and energy intake

Duodenal infusion of lipid alone has been shown to reduce hunger, compared with saline infusion, but does not appear to affect the perception of fullness (115), while gastric distension alone reduces hunger and increases fullness (52), suggesting that input from mechanical distension is required for the induction of fullness. Moreover, the effects of distension on both hunger and fullness were enhanced substantially by concomitant intraduodenal lipid administration (51, 52). The technique used to execute gastric distensions also allowed quantification of the volumes and pressures at which fullness occurred during the distension, by recording volumes and pressures in the intragastric bag (**Figure 3**). The response to lipid varied according to the caloric load administered. At the load of 1 kcal/min, fullness occurred at a higher volume, but lower pressure, when compared with saline, and this reflected relaxation of the gastric wall. In contrast, at the load of 2 kcal/min, fullness was

reported at a volume comparable to that during saline, however, the pressure was substantially reduced (49). In addition, the quality of the sensations varied. Gastric distension during infusion of saline, or lipid at 1 kcal/min, induced predominantly a pressure sensation. In contrast, during infusion of lipid at 2 kcal/min, fullness during gastric distension was reported by the volunteers to resemble a more "meal-like" sensation. And these differences occurred despite the stomach being in a similarly relaxed state, as indicated by identical pressure-volume curves (49). Thus, at the higher load lipid modulated the ability to tolerate gastric distension as well as the quality of the experience of distension.

To our knowledge, the effect on energy intake in the presence of experimental gastric distension and duodenal lipid has not been evaluated, most likely because of the challenging and somewhat invasive nature of the experimental conditions. However, one very elegantly designed study (95), combining a low-nutrient, orally ingested preload (providing the gastric distension stimulus) with a duodenal lipid infusion, demonstrated that the combination of these two stimuli suppressed hunger, and increased fullness, prior to a test meal, and reduced energy intake from the test meal, more than the individual stimuli. Thus, the two stimuli also interact to modulate food intake. Further research in this area is warranted to establish whether, and how, these stimuli could be effectively applied in practice to modulate food intake in the clinical setting, e.g. in obese individuals.

2.3.2. Potential mechanisms mediating the effect of duodenal lipid during gastric distension

Duodenal lipid increases plasma CCK concentrations in a dose-related manner (48), intravenous infusion of the CCK-A antagonist, loxiglumide, slightly increases food intake (12), and CCK mediates, at least in part, the effects of intraduodenal lipid on food intake (95). Thus, CCK may also be involved in regulating the effects of duodenal lipid on gastric

perceptions induced by gastric distension. In support, in a study in healthy human volunteers, combining distension of the stomach with a water-filled bag (500 ml) with intravenous CCK-8 infusion, CCK-8 increased the ratings for fullness induced by the balloon distension, in the absence of a change in intragastric pressure. Moreover, relative to the increase in intragastric pressure, fullness increased, and hunger declined, more steeply when CCK-8 was infused (100), reflecting the pattern of responses observed during duodenal lipid (48, 49) and providing evidence, as the authors of the study concluded, that CCK sensitized the stomach to gastric distension. The hypothesis that if CCK plays a key role, then a nutrient that does not have a major CCK-secretory effect (e.g. carbohydrate) would not be able to mimic the effects of lipid, and the CCK-A receptor antagonist, dexloxiglumide, would substantially reduce the effect of lipid, was investigated in a small number of studies (47, 49) (**Figure 3**). Thus, a study combining gastric distension with an intraduodenal infusion of maltodextrin, at a load of 2 kcal/min, found that while the intrabag volume at which fullness was reported during distension was slightly higher, the pressure at which fullness occurred was lower, during maltodextrin than during saline, due to gastric relaxation (49). The pressure during maltodextrin was also significantly higher than during lipid when given at the same caloric load of 2 kcal/min. These data, therefore, suggest that maltodextrin does not have the same sensitizing effect as lipid. Moreover, a study using the CCK-A receptor antagonist, loxiglumide, found that loxiglumide did not affect the volume, but significantly increased the pressure, at which fullness was reported during concomitant lipid infusion (47). In addition, loxiglumide changed the quality of fullness from a “more meal-like” experience to a predominantly pressure-like sensation, demonstrating that CCK through action on CCK-A receptors mediates, at least in part, the effect of intraduodenal lipid on gastric perception of distension as well as the experience of meal-related sensations. It would be important to investigate the relevance of these findings in the context of meals with differing

macronutrient content, however, in the absence of a CCK-A receptor antagonist for human use, this is unfortunately not possible at this time.

2.3.3. Role of gastric and small intestinal inputs following meal ingestion

It is important to relate the findings discussed in the sections above to the responses that have been observed following oral meal intake. In addition to the contribution from gastric and small intestinal inputs, signals arising in the oral cavity also play a role. Indeed, a number of studies have demonstrated key roles for the contributions of each of these signals to the modulation of gastrointestinal functions and appetite following normal meal ingestion. For example, when tomato soup (400 kcal) was either ingested orally, administered into the stomach, or infused into the duodenum at a rate reflecting gastric emptying, in healthy, lean volunteers, oral ingestion was associated with the greatest suppression of hunger and the desire to eat (31). Moreover, gastric emptying of the soup was slower when ingested orally, compared with intragastric infusion (31). Since energy intake was not evaluated, it is unknown whether these effects, particularly as a result of oral inputs, would also translate into greater energy intake suppression. A recent study in healthy volunteers, in which chocolate milk (~423 kcal) was ingested orally or administered directly into the stomach, confirmed the findings on appetite (133). However, in this study, intragastric administration elevated plasma CCK and insulin, and suppressed ghrelin, more than oral ingestion, while, despite these differences, energy intake at a subsequent meal did not differ on the two days (133), suggesting that either ingestion of a palatable drink may override any contribution from oral stimulation to suppress energy intake or the oral signal did not play a major role in the control of energy intake in this study paradigm. A separate study from the same investigators evaluated the central representation of oral and intragastric inputs during ingestion of chocolate milk (132) and found that intragastric infusion increased activation in the midbrain,

amygdala, hypothalamus and hippocampus, regardless of whether chocolate milk or water was given, presumably an effect of gastric distension. In addition, oral ingestion of chocolate milk was associated with greater activation in the thalamus, amygdala, putamen and precuneus, areas involved in the signaling of reward and gustation (132). Thus, while these data provide evidence that oral consumption is associated with greater activation of intake-related brain areas than intragastric administration, it remains difficult to reconcile these findings with the lack of difference in energy intake between oral and intragastric consumption described above using the same study design (133). Further research is required to clarify the relative roles of oral, gastric and small intestinal inputs utilizing meals with different macronutrient compositions and physicochemical properties.

It is also important to consider the relevance, and translatability, of the potent effects of intraduodenal lipid, discussed earlier, relative to other nutrients in meal situations. When liquid test meals containing either lipid, glucose or a 1:1 mixture of lipid and glucose were given intragastrically, there were no differences in their effects to increase fullness, reduce hunger or energy intake 90 min after nutrient administration (29), suggesting that gastric distension, in the absence of any major differences in gastric emptying, was the main driving force underlying the observed effects. Similarly, when administered into the stomach, high-fat and high-carbohydrate soups (400 kcal) suppressed hunger comparably, and there were no differences in their rates of gastric emptying, assessed using scintigraphy, or on energy intake evaluated 135 min after soup ingestion (30). In contrast, when these soups were consumed orally, the high-fat soup, which emptied from the stomach in this situation more slowly, increased fullness, and reduced hunger, more than the high-carbohydrate soup, and the high-fat soup also tended to reduce energy intake from the subsequent meal more (30). A recent study from our lab confirmed these findings using realistic, pasta Bolognese-based, solid

meals (21). In this study, in which healthy volunteers ingested high-fat, high-carbohydrate and high-protein meals, energy intakes 180 min later were significantly lower following the high-fat and high-protein meals compared with the high-carbohydrate meal, with no significant difference between the high-fat and high-protein meals (21).

Thus, collectively, these data suggest that the appetite- and energy intake-suppressant effects of isolated oral, gastric and small intestinal stimuli are maintained in meal situations. However, whether the magnitudes of these effects are comparable requires further research. This is relevant when considering any potential therapeutic applications. Unless a specifically designed test meal or treatment approach can reduce energy intake in excess of its own caloric content, and, thus, result in an energy deficit, not only acutely, but in the longer-term, it may be more beneficial to utilize the targeted delivery of specific stimuli (gastric distension, e.g. as a low-calorie drink; specific nutrients) in isolated forms. However, much more research is required in this area to develop such approaches and establish their long-term benefits.

3. IMPLICATIONS OF ALTERED SMALL INTESTINAL SENSITIVITY TO UPPER GASTROINTESTINAL STIMULI

While sensory inputs from gastric distension and lipid in the small intestinal lumen are critical for the modulation of gastrointestinal functions, appetite and meal-associated sensations and meal intake, as discussed, there is growing evidence that the sensing of these stimuli can be disturbed in certain eating-related disorders, associated, on the one end of the spectrum, with overeating, for example in obesity (131), and, on the other, the experience of severe digestive symptoms and the inability to complete normal-sized meals (142).

3.1. Obesity – a role for compromised upper gastrointestinal sensitivity?

Higher energy and food intakes, and greater consumption of energy-dense, high-fat foods, in the obese suggests that obese may have a greater capacity to ingest larger amounts of food, possibly due to a reduced ability of the upper gastrointestinal tract to sense incoming signals.

3.1.1. Role of enhanced gastric capacity

A small number of studies have evaluated the hypothesis that obese individuals have a greater gastric capacity, as measured by fasting gastric volumes (2), or by gradually filling a bag positioned in the stomach with air or water (63, 66), or by ingestion of water, or a mixed-nutrient liquid, at defined rates, until fullness, or maximum tolerated volume, was reached (2, 33, 98). For example, obese individuals have been found to have greater fasting gastric volumes (2), tolerate substantially greater intragastric bag volumes (66), or consume larger amounts of water or total caloric loads during so-called water load (98) or nutrient drink tests (2), respectively. While an earlier study found no relationship between the gastric capacity and food intake, the study was very small including only 4 lean and 4 obese volunteers (62, 64). Another study reported that although both a greater BMI and a greater fasting gastric volume were associated independently with lower satiation, BMI was not related to gastric volume (41). A recent, and probably the largest, laboratory-based study performed in this field in 509 normal-weight, overweight or obese individuals, demonstrated that ingestion of a greater volume of a caloric mixed-nutrient liquid was required to reach fullness in the obese, when compared with the normal-weight controls (2). Finally, in one study, dietary restriction for 4 weeks, by means of a very-low calorie, liquid formula diet, resulting in weight loss of ~9 kg, was associated with a reduced gastric capacity (63). This is in contrast with a recent study (2), in which obese subjects underwent treatment with phentermine-topiramate for 2 weeks, and, apart from a reduction in caloric intake, no differences were found in fasting or postprandial gastric volumes, however, the intervention period was shorter, and the subjects

only lost ~1.4 kg in body weight. Thus, while it appears that obesity is associated with changes in gastric function, relating to its capacity, or sensitivity, or both, much more research is required to increase our knowledge in this field, to confirm, or refute, available data using rigorous study designs, to establish conditions under which gastric functions are changed (e.g. depending on particular dietary habits), and, if confirmed, establish underlying mechanisms to utilize these for the development of novel approaches for the management and treatment of obesity (26, 109).

3.1.2. Role of compromised small intestinal sensitivity to fat

While the pathogenesis of obesity is clearly multifactorial, the abundance, and over-consumption, of high-fat, energy-dense foods is an important contributor to the current obesity epidemic (19). The addition of fat to a meal enhances its palatability and improves its texture and "mouth-feel", and, in this way, facilitates overconsumption. Moreover, earlier studies reported that obese individuals appear to have an increased preference for fatty foods (99), and that the proportion of dietary fat was higher in obese, when compared with lean, individuals (102, 104, 138). The mechanisms underlying the association between fat intake and obesity remain to be elucidated, however, under *ad-libitum* conditions, individuals tend to consume a relatively fixed amount of food. Thus, covert manipulation of the energy density of a meal by increasing the fat content will lead to passive overconsumption (15, 85). For example, covert manipulation of the dietary fat content (by increasing the contribution from fat to total energy intake from 30-35% to 45-50%) for 2 weeks led to an increase in energy intake by approximately 15%, associated with increased body weight in normal-weight people (85). Moreover, this effect may be more pronounced in obesity (119, 131). Thus, obese volunteers consumed a significantly greater amount of energy from a meal following a high-fat test preload than the lean controls, while their energy intakes did not differ following

the low-fat test preload (131). Moreover, while lean individuals felt less hungry, and reduced their energy intake at a subsequent meal after ingestion of either a high-fat or a high-protein, when compared with a high-carbohydrate, test meal, the satiating effect of the high-fat test meal was absent in the obese individuals, who only reduced their intake in response to the high-protein meal (21). Collectively, obese individuals appear to be less able to "sense", or detect, the fat content of a meal, thus, obesity may be associated with a reduced sensitivity specifically to the satiating effects of fat.

There is limited, albeit somewhat inconsistent, evidence that the responses in the upper gastrointestinal functions to food, that contribute to intake regulation in healthy, lean individuals, as discussed, may be altered in obesity. While reports from many studies on gastric meal emptying have been inconsistent, with gastric emptying found to be faster, slower or unchanged in obesity (107), the discrepancies are likely to be attributable to a range of factors, including small sample sizes, as well as differences in the previous dietary patterns of participants in the various studies, study designs and methodological approaches (reviewed in (86)). In contrast, in a large study of 328 individuals, gastric emptying of both liquids and solids were found to be accelerated in obesity (2), leading to enhanced exposure of the small intestine to nutrients, including fat, and suggesting that the negative feedback mechanisms elicited by nutrients in the small intestinal lumen may be compromised. In support, we found recently that the pyloric motor response to intraduodenal infusion of oleic acid was markedly reduced in obese individuals when compared with healthy controls; indeed, the magnitude of stimulation of pyloric pressures was inversely related to BMI (138). The diminished pyloric responses to intraduodenal fat may, thus, underlie the accelerated gastric emptying in obesity, and, importantly and given the recently described key role for pyloric pressures in determining subsequent suppression of energy intake, indicate that aspects of the

gastrointestinal regulation of appetite may be compromised in obesity. To investigate this further, studies evaluating the changes in gastrointestinal function in response to dietary restriction, and the relationship with appetite and energy intake (discussed below), are needed.

There is also some evidence that differences may exist between obese and lean individuals in the gut hormone responses to food, although the available data are also limited and often inconsistent. For example, fasting CCK concentrations have been reported to be increased in obese women (7), and postprandial levels may be increased (7), decreased (70) or similar (23) in obese, when compared with lean, individuals. Both enhanced and reduced postprandial GLP-1 release has been reported in obesity (2, 126, 149). PYY responses to a meal appear to be diminished in obesity (2, 83). Finally, fasting ghrelin concentrations are lower, and there is a reduced postprandial suppression in obese, compared with healthy, subjects (46). Data on the fat-specific effects on gut hormone release in obesity are limited. We found no significant differences in the plasma CCK or PYY responses to intraduodenal oleic acid-infusion between lean and obese subjects, although mean CCK concentrations were somewhat lower in the obese (138). Moreover, there were no major differences in plasma CCK, PYY or ghrelin concentrations in response to a high-fat meal between lean and obese subjects in one study (21), while another found significantly lower PYY concentrations after a high-fat meal in obese, when compared with lean, subjects (11). The available data suggest that obesity may be associated with reduced release of certain gut hormones in response to dietary fat, or, if release is normal, perhaps, a reduced sensitivity to the effects of these hormones. However, this area needs further investigation in rigorously designed prospective studies, using carefully designed and well-characterised meals, and taking into account dietary habits of individuals, before any firm conclusions can be drawn. Taken together, from the limited available data it appears that obesity may be associated with a reduced small intestinal

sensitivity to dietary fat, that is, a diminished ability to detect fat, which may compromise the initiation of appropriate feedback mechanisms, including motor and hormone responses, and these changes may contribute to altered appetite and energy intake, but much more research is required in this area. For example, it remains to be established whether any of the reported changes in gastrointestinal sensitivity in obesity are the result of habitually increased fat or energy intakes, or other behavioural or environmental factors, or due to constitutive differences in physiology. However, there is evidence from studies in healthy humans that dietary modifications, e.g. consumption of a high-fat diet, can reduce the ability of the upper gastrointestinal tract to sense dietary lipid (36), suggesting that dietary factors, including previous patterns of dietary intakes, particularly a high-fat, high-energy diet, may lead to a reduced gastrointestinal sensitivity to lipid in obesity.

3.1.3 Effects of high-fat intake on intestinal lipid sensing

In normal-weight volunteers, consumption of high-fat diets for 3 days to 2 weeks has been reported to be associated with an acceleration of gastric emptying, as well as mouth-to-caecum transit, of high-fat test meals (28, 35, 36), and the pyloric motor response to an intraduodenal lipid infusion was less after a 2-week high-fat diet, when compared with the low-fat control diet (17). The effect on gastric emptying appeared to be specific for fat, since consumption of the high-fat diet did not accelerate gastric emptying of a high-carbohydrate meal (28). In contrast, a study evaluating the effects of ingestion of high-fat, high-carbohydrate or high-protein diets for 2 weeks in normal-weight, overweight and obese individuals found no changes in gastric emptying or fasting or postprandial gastric volumes (108), however, a mixed-nutrient meal was employed to evaluate these outcomes, thus, the nutrient-specific effects on these outcomes remain to be elucidated.

Previous diet also appears to adversely affect gut hormone release in humans. For example, consumption of high-fat diets for 2 - 3 weeks has been found to increase fasting plasma CCK concentrations (87) and the plasma CCK responses to a meal (61); the latter effect may be due to increased gastric emptying, since the plasma CCK response to intraduodenal infusion of lipid does not appear to be altered following a high-fat diet (17), suggesting, particularly in the light of a reduced pyloric response to intraduodenal lipid, a reduced sensitivity to endogenous CCK. In contrast, the sensitivity to exogenous CCK-8 infusion does not appear to be affected following a high-fat diet for 3 weeks (87), i.e. the pyloric motor response was unaltered, however, only one dose of CCK was evaluated in this study. Fasting GLP-1 and PYY concentrations, and the GLP-1 response to intraduodenal lipid, have been reported to be unchanged following 2- or 3-week periods on high-fat diets (17, 87), while the PYY response to intraduodenal lipid has not been evaluated. Interestingly, following a 3-week high-fat diet, no differences were found in baseline ghrelin concentrations, while the suppression of ghrelin in response to a high-fat meal was enhanced by ~18% (118).

A number of these studies also assessed subjective appetite and found reduced fullness and increased hunger in response to the high-fat diet, despite greater overall energy intakes (61, 85). In one study, following consumption of a high-fat diet for 2 weeks, hunger and the desire to eat continued to increase during acute duodenal lipid infusion, while, following the low-fat diet, the initial rise in these perceptions was suppressed during the course of the lipid infusion (17). While the limited existing data suggest that consumption of a high-fat, high-energy diet is associated with a reduction in the small intestinal sensitivity to nutrients, particularly lipid, which may then lead to the observed increases in appetite and energy intake (17, 61, 85), much more research is required in this area, including longer-term studies, and studies addressing the specificity of the observed effects for dietary fat and whether the

effects that have been reported are due to very high fat contents in the test diets used or whether these can be replicated in response to diets with more moderate fat contents.

3.1.4 Effects of dietary restriction on small intestinal sensitivity to lipid

Since overconsumption of fat appears to reduce (36, 61), and obesity may be associated with a reduced, small intestinal sensitivity to lipid, particularly oleic acid (138), as discussed above, it is conceivable that dietary restriction may reinstate, at least in part, the sensitivity to lipid, associated with greater gastrointestinal responses to, and energy intake suppression by, small intestinal lipid. An enhanced sensitivity to dietary fat may provide an effective strategy to prevent, or at least reduce, dietary overconsumption, associated with weight loss in the longer-term. However, this does not appear to be widely recognized and, thus, this hypothesis has, to date, only been evaluated in a few small, laboratory-based, clinical studies (22, 129). For example, one study investigated the effects of a 4-day, very-low-calorie diet on the gastrointestinal and appetite responses to an intraduodenal lipid infusion in 8 obese subjects (22). Following the 4-day diet, both the pyloric motor and plasma PYY (but not CCK) responses to intraduodenal lipid were significantly greater, compared with the responses to the lipid infusion in the pre-diet condition (22). In addition, while fasting ghrelin concentrations were much higher following the diet, associated with greater hunger ratings, ghrelin concentrations and hunger ratings were reduced much more during the lipid infusion, than in the pre-diet condition (22). Moreover, despite comparable ghrelin and hunger levels immediately before lunch, i.e. on completion of the intraduodenal infusion, the subjects consumed a smaller amount of food and less energy following the 4-day diet, suggesting that a short period of dietary restriction can indeed enhance the effects of small intestinal lipid on pyloric motility, some hormone responses, appetite and energy intake suppression (22). However, this was an acute intervention corresponding to approximately 70% energy

restriction, so, in a subsequent study, we evaluated the responses to 30% dietary restriction for a period of 12 weeks, in an attempt to better reflect the effects of commonly used, more moderate weight-loss diets and applied for a longer period of time (129). For this purpose, 12 obese men underwent a 12-week 30% dietary restriction. Their gastrointestinal and energy intake responses to intraduodenal lipid infusion, and their body weights, were quantified at baseline, after 5 days, 4 weeks and 12 weeks of dietary intervention (**Figure 4**) (129). We also included 12 healthy lean volunteers as a control group; they were studied during the first 5 days only. At baseline, i.e. immediately before the diet, and 5 days into the dietary restriction period, pyloric stimulation in response to intraduodenal lipid was significantly less than in healthy controls. However, it gradually increased and, at 12 weeks, was significantly greater compared with the early response. A similar effect was apparent for some of the gut hormones, particularly PYY. While there were no significant changes in energy intake in response to intraduodenal lipid, there was a trend for a reduction from week 4, associated with a reduction in body weight over the study period (129). Thus, these data provide the first evidence that the reduced small intestinal sensitivity to duodenal lipid in obese individuals can be altered by dietary restriction, making individuals more sensitive again to the gastrointestinal and appetite-suppressant effects of lipid.

Taken together, the currently available data provide some evidence that in obesity alterations may occur at both gastric and small intestinal levels, including an increased gastric capacity and a reduced ability of the small intestine to detect dietary fat. This may, at least in part, be induced by dietary overconsumption and can, at least partially, be reversed by dietary restriction. A significant research effort is warranted in this field to confirm these findings, and to establish the underlying mechanisms (e.g. by investigating the receptor mechanisms, including changes in their expression or sensitivity, in obesity and in response to dietary

restriction) and pathways to utilize this knowledge for the development of novel preventative and treatment strategies for obesity.

3.2. Functional dyspepsia – associated with enhanced gastrointestinal sensitivity?

Functional dyspepsia is a gastroenterological disorder that affects approximately 10-15% of the population in Western countries. It is characterized by chronic, or recurrent, symptoms originating in the upper gut (particularly the stomach and duodenum). The symptoms, which are triggered by meal ingestion, include epigastric fullness, nausea, epigastric bloating, discomfort and vomiting, and, due to an exaggerated sense of fullness, many patients are unable to complete normal-sized meals, referred to as "early satiation" (143). The symptoms occur in the absence of any apparent organic or structural abnormalities in the upper gastrointestinal tract, although evidence is emerging relating to possible involvement of impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia (148). The reported temporal relationship between symptoms and food ingestion initially led clinicians to believe that functional dyspepsia was due primarily to gastric motor dysfunctions (e.g. delayed gastric emptying), and, subsequently, a range of abnormalities has been described in subgroups of functional dyspepsia patients, including abnormal intragastric meal distribution, impaired proximal gastric relaxation, abnormal antral filling and antral dysmotility, however, any associations between symptoms and any of these abnormalities have been relatively weak (57). It is increasingly apparent that several triggering factors, including diet and lifestyle, genetic factors, early life experience, autonomic dysfunctions, gastrointestinal infections, inflammation or immune activation, gut microbiota, cognitive influences and psychological disturbances, all play some role, although the underlying cause(s) remain essentially unknown (53).

3.2.1 The role of dietary habits and specific foods

Symptom development in many patients is closely related to meal ingestion (13, 114), for example, in response to a very small meal (white bread, an egg and water), containing only 250 kcal, patients with functional dyspepsia experienced the full range of symptoms within 15 - 45 min, while only fullness increased in the healthy volunteers (13). However, despite the frequent reports of patients that their symptoms are related to food ingestion, particularly fatty foods, surprisingly few studies have evaluated dietary habits, and intakes, in functional dyspepsia. There are a number of factors to consider in relation to diet, which might influence symptoms, and these include caloric intake, eating patterns, specific foods or food components, as well as the macronutrient composition of the diet.

Functional dyspepsia patients often report that they only tolerate small meals, so it is conceivable that their caloric intake is reduced, associated with lower body weights. However, data are inconclusive. We found a trend for reduced caloric intake in a small cohort of functional dyspepsia patients using 7-day diet diaries (114). In other studies, varying proportions of patients gained weight or were overweight/obese, were normal-weight, or reported small weight loss (27, 60, 103). A high prevalence of unexplained weight loss was found in some studies, but these patients were recruited in a tertiary referral centre and probably had more severe symptoms (141). Food intake was not measured in any of these studies. Only a few studies have evaluated eating patterns in functional dyspepsia, incl. meal size and frequency, and most had considerable limitations, including being retrospective studies, lacking definitions for meals and snacks and any information of whether patients were symptomatic at the time. Some, but not all, studies found a trend for a higher prevalence of snacking and a lower frequency of meals per day, and no differences in the speed of eating. While a range of foods, and food groups, are reported by patients to induce, or exacerbate,

symptoms, including fried foods, wheat- and carbohydrate-containing foods, carbonated drinks, milk and dairy products, certain vegetables (possibly particularly those containing fermentable oligo-, di-, and monosaccharides and polyols – so-called "FODMAPs" (65)), spicy foods, citrus fruit, coffee and alcohol (53), fatty and "rich" foods, or meals, appear to be implicated particularly frequently, triggering symptoms in >50% of patients, and many patients report to avoid these foods in an attempt to alleviate symptoms (76, 103). Thus, a large, and diverse, range of diet-related factors contributes to symptom induction in functional dyspepsia, making identification of specific dietary culprits very challenging. Data on macronutrient intakes have also been inconclusive (27, 103, 122). Given the short-comings of the existing studies, we evaluated the relationship between symptoms with dietary patterns in a group of patients with functional dyspepsia in a prospective study using detailed food and symptom diaries and applying clear definitions for eating and drinking episodes and symptom categories and their severity. We hypothesised that patients with functional dyspepsia would consume smaller meals and experience more meal-associated symptoms, but eat more frequently, when compared with healthy subjects, and that the occurrence and severity of symptoms would be related directly to the amount eaten and particularly also the amount of fat in the diet (114). Overall, we found no major differences between patients and healthy controls. The patients consumed significantly fewer main meals, and there was a trend for a larger number of light meals and snacks in the patients. Moreover, we obsesrved trends for lower weekly energy, fat and carbohydrates intakes in the patients, but there was substantial variation, so that some patients had much larger intakes than healthy controls (114). The majority of symptoms in the patients (64%) were meal-related, and all typical functional dyspepsia symptoms were experienced widely, on average at a moderate severity, and occurred within 15 - 45 minutes (114). Moreover, we found relationships between symptoms and aspects of dietary intake. Overall meal-associated symptoms were related directly to

energy intake, and inversely to carbohydrate intake, fullness was related directly to energy, fat and protein intakes, and inversely to carbohydrate intake, and bloating was related directly to fat intake (114). These data, therefore, provided, for the first time, strong evidence of relationships between certain dietary factors, particularly the amount of food, or energy, consumed, as well as dietary fat intake, and symptoms in functional dyspepsia. The data also suggested some differences between patients and healthy controls, but also that many patients may not have adjusted their intakes in any way in an attempt to alleviate symptoms, possibly owing to a lack of knowledge as to how their symptoms may relate to specific dietary factors. Further research is required, particularly prospective studies in large cohorts of patients to evaluate the effect of targeted dietary changes on symptom improvement.

3.2.2 Enhanced gastric and small intestinal sensitivity in functional dyspepsia

The inability of many patients to complete normal-sized meals, and the frequent reports by patients that their symptoms are triggered, or exacerbated, by fatty meals, has led to the hypothesis that functional dyspepsia, at least in sub-groups of patients, may be characterized by a hypersensitivity to gastrointestinal luminal stimuli, relating to the mechanical (distension) and/or nutrient (particularly fat) components of a meal (9, 147).

Studies evaluating the gastric sensory responses to gastric distension have revealed that 30-48% of patients indeed exhibit a hypersensitivity to mechanical distension of the stomach (18, 97). Thus, when either the proximal or distal stomach is distended by inflating a bag with air, patients with functional dyspepsia experience discomfort at lower distension volumes or pressures than healthy controls (18, 24). Thus, hypersensitivity to gastric distension may contribute to the inability of patients to complete normal meals. Studies in which lipid was infused directly into the duodenum, or ingested in a low-nutrient soup or in the form of a

palatable high-fat yogurt, have established that ~60-70% of patients with functional dyspepsia are hypersensitive to lipid (8, 71, 113). For example, intraduodenal infusion of lipid, at a load of 1 kcal/min, which is largely unperceived in healthy controls, triggers typical dyspeptic symptoms, including fullness, nausea and bloating, and, furthermore, exacerbates the gastric hypersensitivity to gastric distension, in the patients (8), as evidenced by lower intragastric volumes tolerated by the patients during gastric distension. Moreover, ingestion of appetizing high-fat yogurts resulted in significantly greater nausea and epigastric pain scores than the fat-free, equivolaemic (300 or 400 g) control yogurt (55, 113). The hypersensitivity appears to be specific for fat, since isocaloric duodenal glucose infusion does not induce symptoms (9), and both nausea and pain scores were lower following ingestion of a high-carbohydrate yogurt, that was isocaloric and isovolaemic (400 g) to the high-fat yogurt (113) (**Figure 5**). Interestingly, all test yogurts, including the low-nutrient, low-calorie control, were associated with epigastric discomfort, confirming that volume, and thus gastric distension, per se also plays a role. Taken together, these data suggest that, in addition to a hypersensitivity to gastric distension, hypersensitivity to specifically lipid plays a role in symptom induction in functional dyspepsia, so that food ingestion, eliciting gastric distension, combined with the effects from fat, may induce exaggerated signals in the upper gastrointestinal tract, triggering dyspeptic symptoms. An area that has not been investigated in functional dyspepsia relates to the physiological regulation of appetite. This represents a major challenge, since the experience of symptoms interferes with the normal experience of appetite-related sensations, including fullness after a meal, thus, it remains unknown whether meal, and energy, intake in these patients is determined predominantly by the occurrence of symptoms, or whether, and to what extent, normal appetite-regulatory mechanisms are functional.

3.3. Potential mechanisms underlying the altered gastrointestinal sensitivities in obesity and functional dyspepsia

From the divergent responses to gastric mechanical and small intestinal nutrient stimulation discussed above, obesity and functional dyspepsia may be viewed as disorders at opposing ends of a spectrum in relation to gastrointestinal sensitivity. As such it may be a useful approach to address the question of which potential mechanisms may underlie these disturbances together. It is conceivable that changes in the sensitivity to gastrointestinal hormones may play a role. In this context, and as discussed, exogenous CCK-8 administration, for example, enhances the sensitivity of the stomach to gastric distension (100). However, the limited available evidence indicates that the appetite and energy intake responses to intravenous CCK and PYY do not differ between obese and lean individuals (10, 84), although only one hormone dose was used in each study, and the study using CCK was performed in females only, and did not control for any potential influences of the menstrual cycle (20). In contrast, CCK may play a role in mediating the effects of lipid in functional dyspepsia. A small, laboratory-based study found that CCK-A receptors mediate the effect of intraduodenal fat on symptoms and sensitivity, at least in part, since the CCK-A receptor antagonist, dexloxiglumide, markedly reduces lipid-induced symptoms, and increased the pressure at which discomfort was reported by the patients (50). The role of CCK secretion is currently unclear; the plasma CCK responses to intraduodenal lipid do not appear to differ markedly between patients and healthy controls (50). In contrast, patients have greater mean plasma CCK concentrations in response to oral ingestion of both high-fat and high-carbohydrate yogurt-based test-meals, although only concentrations in response to the high-fat yogurt were significantly higher than those in the healthy controls (113). It is also possible that functional dyspepsia may be associated with an enhanced sensitivity to CCK, since exogenous administration of CCK induces a greater symptomatic response, including

bloating, nausea and fullness, in patients than healthy volunteers (34). The role of other gut hormones, including peptide YY, glucagon-like peptide-1 and ghrelin, which play a role in appetite control, in the induction, or exacerbation, of dyspeptic symptoms is currently unclear (54), and in the absence of specific receptor antagonists for these hormones (with the exception of GLP-1) for use in humans, it is difficult to define the role of these hormones.

It is currently also unknown at what level(s) between the gut and the brain any dysfunctions, or changes, occur, that may underlie the reported altered upper gastrointestinal sensitivities to luminal stimulation by mechanical distension and lipid in obesity or functional dyspepsia. It will be important to study any changes in gastrointestinal mechano- and chemo-receptors (in the case of the latter, particularly fatty acid receptors), including their expression and activation. For example, there is evidence that acute (30 min) small intestinal lipid exposure increases the expression of the G-protein coupled receptor, GPR119, in healthy volunteers (39). Moreover, preliminary data from a recent study in our lab indicate that the expression of GPR120 and the lipid transporter, CD36, are related directly, and expression of GPR119 indirectly, to body mass index, in a small group of lean and obese subjects (88). Potential changes in the central processing of meal-related signals, including both gastric distension and lipid, also need to be considered and studied in detail (146). In this context, the role of cognitive factors should also be considered. For example, it has been shown in patients with functional dyspepsia that both attention (due to anticipatory knowledge) and distraction (by performance of a mental task) can modulate perception of duodenal distension, so that attention increases, and distraction attenuates, gut perception (1). Thus, particularly functional dyspepsia patients may respond with symptoms to certain foods as a result of a previous negative learning experience or information they have received. In support, when patients were informed that a low-fat yogurt was “high in fat”, they reported significantly

greater symptoms of nausea, fullness and bloating, when compared with the condition in which they received the correct information (that is that the low-fat yogurt was “low in fat”) (55); in contrast, symptoms did not differ in the conditions when the patients received the high-fat yogurt, whether they were given the correct information or not (55). Thus, while cognitive factors play a role, potentially particularly with low-fat meals, when the fat content is perceived to be high, the fat content of a meal per se does have an independent effect. How such influences may be involved in the context of modulating gastrointestinal sensitivity to foods also warrants further investigation (69).

Taken together, available evidence suggests that altered sensitivities of the upper gastrointestinal tract to meal-related stimuli appear to occur in obesity and functional dyspepsia. The underlying mechanisms remain largely unknown and require much more research in order to establish whether specifically targeted, nutrient-specific dietary therapies have a role in the management and treatment of these disorders, and to develop effective dietary and/or pharmaceutical therapies.

4. LIMITATIONS

This review outlined the role of meal-associated factors, with a focus on gastric distension and small intestinal (duodenal) exposure to lipid, in the regulation of gastrointestinal perceptions, appetite and energy intake in healthy humans, and explored the changes that occur in two disorders, obesity and functional dyspepsia, which, at opposing ends of a spectrum, appear to be associated with disturbances in the gastrointestinal sensing of these meal-related factors. While the focus was on these two conditions, it is important to recognize that changes in gastrointestinal functions and responses to ingested nutrients, with potential implications for appetite regulation, may occur in a range of settings and disease

states, including across the lifespan (childhood, adolescence, adulthood, old age) (89, 139), across the range of body weights and associated disorders (e.g. anorexia nervosa, bulimia, overweight/obesity) (37, 90, 153), in response to acute (e.g. in trauma patients in intensive care) (32, 105) and chronic (type 2 diabetes, irritable bowel syndrome) (54, 110) illnesses, as well as after obesity-related bariatric surgery (82). While it was beyond the scope of this paper to do the research in these various fields justice by providing detailed reviews, it is important to recognize that insights from these areas will most likely be important to gain a more comprehensive understanding of the mechanisms underlying the gastrointestinal sensing of nutrients, as well as appetite regulation and dysregulation, in order to identify, and develop, novel, and effective therapeutic approaches to these conditions.

In the process of food ingestion, the meal stimulates taste receptors on the tongue, which assess the composition of the meal, as well as its texture and palatability; this information is signalled to the brain and associated with a number of physiological changes, including gastric acid, CCK and pancreatic secretions, as well as receptive relaxation of the stomach immediately after meal ingestion (77, 125), preparing the gastrointestinal tract to receive and process the meal and influencing appetite and energy intake. Bypassing the oral cavity by applying isolated stimuli, including gastric distension and/or intraduodenal nutrient infusion, by definition, excludes any contributions of the oral cavity to the regulation of appetite, and, in the case of duodenal nutrient delivery, also any role for gastric emptying. Moreover, any effects observed in response to administration of nutrients into the duodenum may also be accounted for, at least in part, by nutrients being transported to more distal parts of the small intestine, including the jejunum and ileum, although, in healthy humans, this should only amount to small quantities, particularly in the ileum. Nevertheless, direct administration of nutrients into the jejunum and ileum, albeit often at unphysiologically high loads (up to 4.9

kcal/min), has been found to reduce appetite and energy intake and slow gastric emptying and small intestinal transit (92, 145, 150-152), effects now all attributed to the so-called "jejunal" or "ileal brake" mechanisms. The term "ileal brake" was coined originally to describe the effects of ileal fat infusion on jejunal motility (117, 134, 135). Taken together, in order to understand the gastrointestinal mechanisms that contribute to meal-induced appetite regulation, clearly all the contributions from the different regions need to be considered. However, if the focus is on utilizing a particular aspect, for example, to develop a novel approach to obesity and weight management, the targeted delivery of nutrients to specific regions of the gut, most likely involving novel delivery mechanisms, may be more relevant because of its greater potency (3). A substantial research effort in this field is still required, and warranted.

5. SUMMARY AND OUTLOOK

This review has summarized current knowledge on the role of signals that arise from the upper gastrointestinal tract in response to meal ingestion, with a focus on gastric distension and the presence of lipid in the small intestine, in the modulation of gut functions, including gut hormone release and modulation of gastrointestinal motility, induction of gastrointestinal and appetite-related sensations, and the suppression of energy intake. While the role of gastric factors, including gastric distension, is relatively transient, although important, the contribution from nutrients, as they are gradually transferred from the stomach to the small intestine in the process of gastric emptying, can continue for hours. The signal elicited by duodenal lipid also potently interacts with gastric distension to modulate its conscious perception and the quality of the sensation it induces. There is evidence that the sensitivity of the upper gastrointestinal tract to these stimuli can be disturbed, so that their effects are either compromised, as may be the case in obesity, or amplified, as is the case in functional

dyspepsia. In obesity, there is evidence of an enhanced gastric capacity, and preliminary evidence suggests that the small intestinal sensing of lipid may be reduced, associated with reduced gut responses and compromised inhibition of subsequent energy intake. These findings warrant further investigation in larger cohorts, including research on the locations (central and/or peripheral) and neural pathways involved in, and the molecular mechanisms underlying, these changes. It is also unknown whether reduced gastrointestinal sensitivity to lipid is a cause of obesity, or the result of dietary overconsumption of high-energy, high-fat foods, although evidence that points towards a role for diet comes from studies that have established that overfeeding normal-weight individuals can induce changes reminiscent of small intestinal hyposensitivity to lipid, and dietary restriction can reinstate, at least in part, small intestinal lipid sensitivity. Functional dyspepsia, on the other hand, is associated, in up to 2/3 of patients with pathophysiologically enhanced sensitivities to both gastric distension and small intestinal lipid, and the available evidence suggests that these disturbances may, at least in part, explain the patients' frequently reported inability to complete normal-sized meals and intolerance of foods, or meals, rich in fat. Much more research is required to establish the origins of, and mechanisms underlying, these hypersensitivities, and how the findings can be translated into effective therapeutic strategies.

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FIGURE LEGENDS

Figure 1: Effects of intraduodenal lipid infusion on upper gastrointestinal motility in healthy humans. (A) The presence of lipid in the small intestinal lumen is associated with well-coordinated changes in the motor activity of the stomach and small intestine, including relaxation of the proximal stomach, suppression of antral and duodenal pressure waves, and stimulation of tonic and phasic pressures in the pylorus, providing a marker for gastrointestinal luminal nutrient sensing. Together these effects underlie the slowing of gastric emptying of a meal. (B) Typical recording of antropyloroduodenal pressures, during fasting (left panel), showing so-called phase III activity moving distally, with pressure waves at the maximum frequency, followed by a phase I, a period of motor quiescence. In contrast (right panel), the motor pattern in response to duodenal lipid infusion, with a suppression of antral and duodenal pressure waves and stimulation of regular pyloric pressure waves. P, pylorus.

Figure 2: Schematic representation of the experimental approach used to apply gastric distension and intraduodenal nutrient stimuli in a standardized manner in humans. A nasoduodenal catheter is inserted through the nose and positioned with the tip located in the duodenum, and used for the infusion of nutrient or control solutions. Then, the volunteers swallow a second catheter, which has a very thin, flaccid bag tightly wrapped around its distal end. The bag is unfolded once the catheter is correctly positioned within the stomach. The catheter is then connected to an electronic barostat, which delivers defined volumes or pressures into the bag, and, in this way, distends the stomach. LES, lower (o)esophageal sphincter.

Figure 3: Volume (left panels) and pressure (right panels) thresholds, at which fullness occurred during gastric distension in healthy volunteers, (A) in response to intraduodenal saline control (S) or increasing loads of lipid at 1 (L-1) and 2 (L-2) kcal/min (49), (B) in response to intraduodenal saline (S) or carbohydrate (maltodextrin) at 2 kcal/min (M-2) (49), and (C) in response to intraduodenal saline (S) or lipid (L) at 2 kcal/min, with (S-Lox, L-Lox) or without (S-P, L-P) the CCK-A receptor antagonist, loxiglumide (47). Data are expressed as a percentage of the response during the control condition, and are means ± SEM. Significantly different ***** from respective saline control, # from respective saline control and other lipid condition; $P < 0.05$. L, lipid, M, maltodextrin, P, placebo, Lox, loxiglumide.

Figure 4: Effects of 30% dietary restriction for 12 weeks on the gastrointestinal (pyloric pressure, A) and energy intake (B) responses to intraduodenal lipid infusion, and on body weight (C) in healthy, lean individuals at baseline (BL, calculated as the mean of data from days 0 and 5), and in obese individuals on day 0 (D0, i.e. immediately before commencement of the diet), on day 5 (D5), and at the end of week 4 (W4) and week 12 (W12) of the diet (129). Significantly different ***** from baseline in lean controls, # D0 and D5; $P < 0.05$. Data are means ± SEM.

Figure 5: Scores for nausea following ingestion of 400 g palatable, yogurt-based test meals, including a low-nutrient control meal (180 kcal) (left panel), or isocaloric (500 kcal) high-carbohydrate (middle panel) or high-fat (right panel) test meals, in patients with functional dyspepsia and healthy controls (113). Significantly different ***** from control, # from high-CHO, **Ω** from healthy controls; $P < 0.05$. CHO, carbohydrate. Data are means ± SEM.