Gastrointestinal fat sensing – implications for appetite regulation and disorders of impaired GI nutrient sensing

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The gastrointestinal tract plays a critical role in the regulation of both subjective perceptions of appetite as well as acute energy intake. We have demonstrated recently that the magnitude of the stimulation of pyloric pressures and gut hormones, particularly cholecystokinin (CCK), are independent determinants of subsequent energy intake in healthy, lean humans. These effects are initiated by the interaction of nutrients with receptors located in the oral cavity and the mucosa of the upper gastrointestinal tract. Thus, dietary nutrients, particularly lipid, have potent effects to modulate gastric relaxation and pressures in the antropyloroduodenal region, associated with slowing of gastric emptying, and to stimulate the release of gut peptides, including CCK, glucagon-like peptide-1 and peptide YY, and to suppress ghrelin, culminating in the suppression of appetite and energy intake.

It is increasingly recognized that the gastrointestinal sensitivity to lipid may be compromised in a number of disorders, associated wit a diverse range of eating-related disorders, including obesity and functional dyspepsia. Obesity, on the one hand, appears to be characterized by a reduced sensitivity to the gastrointestinal and appetite-suppressant effects of fat. For example, ingestion of a high-fat meal reduces subsequent energy intake in lean, but not in obese, subjects, when compared with a high-carbohydrate meal. This may be due to a desensitization of both oral and gastrointestinal mechanisms to the effects of lipid, so that obese subjects have increased oral detection thresholds for fat, and both the gut hormone and motility responses to intraduodenally administered fat are lower in obese, compared with lean, subjects, associated with higher energy intakes. A high dietary fat intake is, at least in part, responsible for these detrimental changes, since consumption of a high-fat diet decreases taste sensitivity to oleic acid and the gastrointestinal and appetite responses to intraduodenal lipid in lean subjects. Conversely, a low-fat, low-energy diet, increases taste sensitivity to oleic acid in both lean and overweight/obese subjects, and enhances the effects of intraduodenal lipid on gastrointestinal hormone release, antropyloroduodenal motility and energy intake suppression in obese subjects. Thus, both oral and duodenal sensitivity to lipid can be modulated potently by dietary fat content. Therefore, innovative therapies that may increase gastrointestinal sensitivity to dietary nutrients, particularly fat, may help to effectively regulate energy intake and, thus, body weight.

At the other end of the spectrum, a sub-group of patients with functional dyspepsia suffer from symptoms of nausea, bloating, early fullness and the inability to complete a normal-sized meal, in response to even small amounts of food, particularly foods rich in fat. Our research has shown that these patients have enhanced sensitivities of the stomach to distension and of the small intestine to lipid. In addition, the presence of lipid in the small intestinal lumen further exacerbates gastric mechanical sensitivity. The nutrient hypersensitivity appears to be specific to fat, since intraduodenal glucose does not have the same effect, while the effects of protein have not been evaluated. The effects of fat on gastrointestinal mechanical and chemical hypersensitivity can be reduced by co-administration of the lipase inhibitor, orlistat, which prevents fat digestion, and, thus, the release of fatty acids in the small intestinal lumen. Furthermore, i.v. administration of the CCK_1 receptor antagonist, dexloxiglumide, or oral ingestion of the $5\text{-}HT_3$ receptor antagonist, ondansetron, also improve hypersensitivity and the symptomatic response to lipid in patients with functional dyspepsia. This suggests that a sub-group of patients with functional dyspepsia are hypersensitive to intraluminal fatty acids, and that gastrointestinal CCK_1 and $5\text{-}HT_3$ receptors, most likely amongst others, mediate these effects. The location(s) of the defect in gastrointestinal sensitivity are currently unknown.

In summary, intact gastrointestinal luminal nutrient sensing is critical for the normal regulation of appetite and energy intake. This signaling is deregulated in a number of disorders, associated with changes in gut perceptions, appetite and gastrointestinal symptoms, as well as energy intake. A better understanding of the underlying mechanisms will be critical for the development of novel, nutrient-based as well as pharmacological treatment approaches for disorders associated with changes in gastrointestinal nutrient sensitivity.