VISCERAL PERCEPTION

The role of fat and cholecystokinin in functional dyspepsia

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The main factors involved in the pathophysiology of fat induced dyspepsia were investigated by reviewing a series of controlled double blind randomised studies which sought to determine the role of nutrient fat and the postprandial release of cholecystokinin (CCK) in the development of dyspeptic symptoms in healthy volunteers and in patients with functional dyspepsia. The studies showed that during distension of the stomach, lipids are a major trigger of dyspeptic symptoms such as nausea, bloating, pain, and fullness, and that they modulate upper gastrointestinal sensations and symptoms in a dose related fashion. CCK is a major mediator of the sensitisation of gastric perception by lipids in patients with functional dyspepsia as the CCK-A receptor antagonist dexloxiglumide markedly diminishes this effect. The studies provide important insights into the mechanisms underlying gastrointestinal perception in response to fat and the role of CCK in patients with functional dyspepsia.

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SUMMARY

A subgroup of patients with functional dyspepsia are characterised by heightened visceral sensitivity to mechanical distension of the stomach with a balloon. Small intestinal infusion of nutrients, particularly fat, exacerbates this hypersensitivity and also modulates sensations, such as hunger and fullness, in healthy subjects. Previous studies in healthy subjects suggest that cholecystokinin (CCK)-A and serotonergic (5-HT_3) receptors mediate, at least in part, the effects of lipid on gastrointestinal sensations. Recent studies have shown that duodenal fat infusion causes a dose dependent increase in the intensity of sensations and symptoms during gastric distension. However, fat digestion, achieved by using the specific lipase inhibitor tetrahydrolipstatin (THL) is necessary to promote the effects of fat on visceral sensation, gastric relaxation, and CCK release. The digestion products of fat interact with receptors in the small intestine. Long chain triglycerides (LCT) appear to be more potent than medium chain triglycerides (MCT) in inducing symptoms of fullness, nausea, and suppression of hunger. The effects of LCT are at least partially mediated by CCK as MCTs do not cause CCK release. In patients with functional dyspepsia, gastrointestinal symptoms induced by duodenal lipid infusion and gastric distension are alleviated by the CCK-A receptor antagonist dexloxiglumide. These studies provide important insights into the mechanisms underlying gastrointestinal perception in response to fat and the role of CCK in healthy subjects and patients with functional dyspepsia.

INTRODUCTION

Patients with functional dyspepsia exhibit a variety of symptoms, such as bloating, nausea, and early fullness, which generally occur in response to ingestion of a meal. Hypersensitivity of the stomach to postprandial distension is an essential pathophysiological characteristic of functional dyspepsia and an important factor in the generation of dyspeptic symptoms.[1 2] In healthy subjects and in patients with functional dyspepsia, perception of gastric distension is enhanced by nutrient lipids but not by glucose (fig 1).[3–5]

A number of studies have shown that release of CCK in response to fat ingestion plays a major role in the regulation of upper gastrointestinal function.[6–9] Fat induced CCK release inhibits postprandial gastric emptying by altering gastric motility,[6 7] and the products of fat hydrolysis inhibit postprandial gastric acid secretion, probably by modifying CCK release.[9]

It can therefore be hypothesised that besides their effects on upper gastrointestinal function, such as gastric emptying, stimulation of pancreaticobiliary secretion, and gastric acid secretion, fat induced CCK release plays an important role in the pathophysiology of functional dyspepsia. Knowledge of the factors involved in the generation of fat induced symptoms is essential for the development of therapeutic concepts and targets in the treatment of functional dyspepsia. We therefore sought to investigate the main factors involved in the pathophysiology of fat induced dyspepsia in a series of controlled double blind randomised studies.

In all trials, a standard barostat technique was employed to study gastric volume changes and to apply ramp distensions of the proximal stomach,[10] with and without concomitant intraduodenal infusion of nutrients and drugs. Most studies were performed in healthy volunteers,[11–14] and in one trial, patients with functional dyspepsia were examined.[15] Sensory responses were assessed by means of visual analogue scales.

The role of intestinal chemoreceptors thought to be involved in mediating the effects of lipids

Abbreviations: CCK, cholecystokinin; LCT, long chain triglycerides; MCT, medium chain triglycerides; SPE, sucrose polyester; THL, tetrahydrolipstatin.

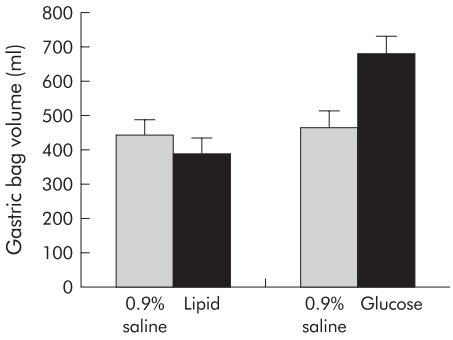

Figure 1 Gastric bag volumes at which discomfort was experienced by patients with functional dyspepsia during gastric distension and duodenal infusion of saline, lipid, or glucose (1 kcal/min). Patients tolerated significantly larger volumes during gastric distension when glucose was infused compared with saline, most likely due to the greater gastric relaxation that was observed during glucose infusion. However, despite marked gastric relaxation during the lipid infusion, discomfort was experienced during this infusion at similar volumes as during saline infusion, indicating heightening of gastric sensitivity to distension by lipid.

was investigated in healthy volunteers during duodenal infusion of benzocaine combined with lipids.[13] The relationship between the energy load of nutrients, in particular fat, and the sensory responses to gastric distension was investigated by administering increasing amounts of intraduodenal nutrients.[11] The effects of digested (as opposed to undigested) fat on induction of dyspeptic symptoms was studied using the specific lipase inhibitor orlistat (tetrahydrolipstatin (THL)) to inhibit triglyceride hydrolysis during intraduodenal infusion of lipids.[14] In order to evaluate the role of CCK in the pathophysiology of functional dyspepsia, generation of dyspeptic symptoms and CCK release was studied in patients with functional dyspepsia using increasing doses of duodenal lipids combined with intravenous dexloxiglumide, a specific CCK-A receptor antagonist.[15]

BLOCKADE OF SMALL INTESTINAL RECEPTORS WITH BENZOCAINE

CCK-A and 5-HT_3 receptor antagonists have been shown to modulate gastric perception and to reduce the occurrence and intensity of nausea.[16 17] These findings suggest that small mucosal chemoreceptors in the small intestine are involved in the effects of duodenal lipids on gastric sensory function. Luminal (duodenal and jejunal) infusion of the local anaesthetic benzocaine or saline combined with duodenal infusion of lipid or saline was used to investigate the role of intestinal chemoreceptors in the induction of gastric sensations by lipid in healthy volunteers.

Benzocaine attenuated duodenal lipid induced gastric relaxation and markedly diminished CCK release in the duodenum but not in the jejunum. Benzocaine also diminished the generation of dyspeptic symptoms and nausea that accompanied duodenal infusion of lipids and gastric distension. During duodenal lipid infusion, gastric perception appeared to be disassociated from gastric relaxation. These studies demonstrate that duodenal receptors activated by lipids play an important modulatory role in the induction of gastrointestinal sensations during gastric distension. Application of topical anaesthetic drugs may therefore provide one possible therapeutic approach to the treatment of functional gastrointestinal disorders.

DOSE-RESPONSE RELATIONS BETWEEN DUODENAL LIPID LOADS AND GASTRIC PERCEPTION

Duodenal lipids induce nausea during gastric distension and enhance gastric relaxation. Previous studies suggested that increasing the dose of lipids increases the severity of nausea.[3] It is conceivable therefore that increasing amounts of lipids augment gastric relaxation and induce dyspeptic symptoms in a dose dependent fashion. To test this hypothesis, the relationship between increasing intraduodenal doses of lipids (1–3 kcal/min) or saline and gastric sensations during gastric barostat distension was studied in healthy volunteers.[11]

Nausea and other dyspeptic symptoms were found to increase during gastric distension in relation to the dose of lipid administered. Lipid administration simultaneously caused a dose dependent relaxation of the stomach and an increase in plasma concentrations of CCK. Duodenal lipids without gastric distension did not significantly modulate gastrointestinal sensations.

These studies highlight the importance of the interaction between mechanical and chemical stimuli in the upper gastrointestinal tract for the generation of postprandial

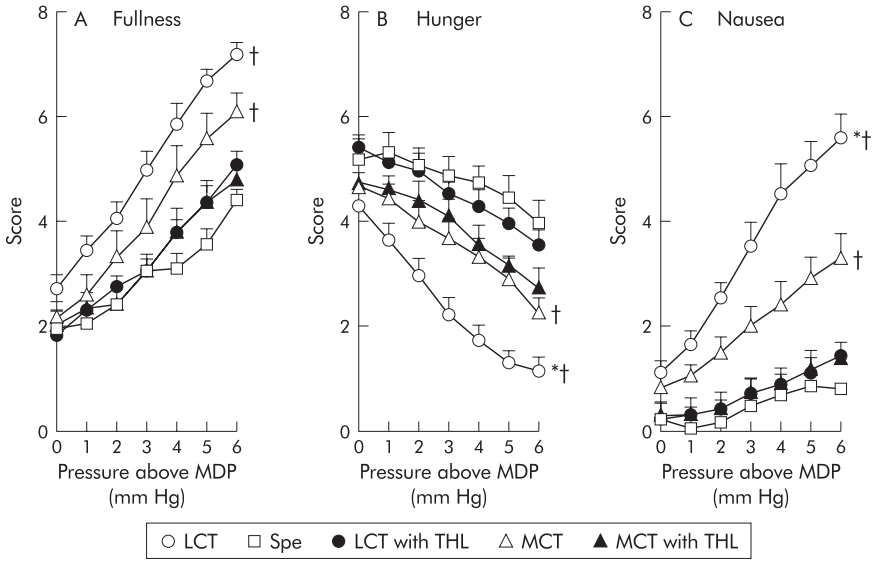

Figure 2 Scores for fullness (A), hunger (B), and nausea (C) during isobaric gastric distension and duodenal infusion of different fat emulsions. LCT, long chain triglycerides; MCT, medium chain triglycerides; Spe, sucrose polyester; THL, tetrahydrolipstatin; MDP, minimum distending pressure. *p<0.05, LCT versus LCT with THL; †p<0.05 versus Spe.

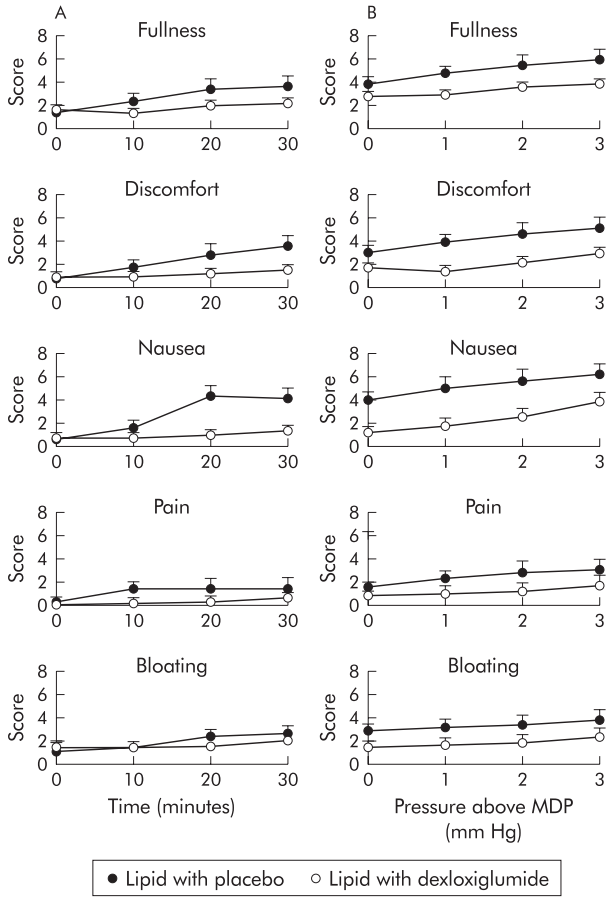

Figure 3 Scores for dyspeptic symptoms in patients with functional dyspepsia during duodenal infusion of 20% lipid given with intravenous placebo or dexloxiglumide (A). Infusions were combined with gastric distension (B). MDP, minimum distending pressure.

sensations and symptoms in humans. The pronounced effects on gastric relaxation, CCK release, and subjective sensations appear to be specific to fat as other macronutrients—that is, carbohydrates and protein—have a much less pronounced effect on these parameters.[5 12]

THE ROLE OF FAT DIGESTION IN THE MODULATION OF POSTPRANDIAL GASTROINTESTINAL SENSATIONS

The biological effects of triglycerides (for example, the release of CCK or stimulation of pancreaticobiliary secretions) are dependent on the hydrolytic digestion of fat to fatty acids.[7–9] It was previously unknown whether enhancement of gastric perception by duodenal fat also depends on hydrolysis of triglycerides. Moreover, the effect of different chain lengths of fatty acids on gastric perception is still poorly understood.

The effect of intraduodenal infusion of emulsions containing long chain triglycerides (LCT) or medium chain triglycerides (MCT) given with and without THL was investigated in healthy volunteers. Gastrointestinal sensations and plasma CCK release were assessed before and during gastric distension. LCT was found to induce gastric relaxation with a more pronounced effect than MCT. THL completely abolished the response to both emulsions. Interestingly, only LCT caused a rise in plasma CCK levels which was absent during THL infusion. Gastrointestinal sensations, such as nausea and fullness, increased more with LCT than with MCT (fig 2). THL markedly diminished the intensity of these sensations. Sucrose polyester (SPE), an indigestible fat used as a control infusion, had no effect on gastric volume or the generation of dyspeptic symptoms. LCT suppressed hunger more than MCT. THL abolished this effect only during LCT infusion but had no effect on hunger scores during MCT or SPE infusion.

These findings show that fat digestion is an essential step in the modulation of gastrointestinal sensations by fat during gastric distension. The modulatory function of fat on gastrointestinal sensitivity may be partially mediated by release of CCK.

THE ROLE OF CCK-A RECEPTORS IN THE PATHOPHYSIOLOGY OF FUNCTIONAL DYSPEPSIA

Previous studies indicate that intravenous administration of a CCK-A receptor antagonist reduces the effects of duodenal lipid on gastric relaxation and gastrointestinal sensations during gastric distension.[16] The release of CCK may therefore be a contributing factor to dyspeptic symptoms after fat ingestion. The role of fat induced CCK release in the pathophysiology of functional dyspepsia was studied by investigating symptoms and plasma CCK levels following increasing doses of duodenal lipids and gastric distension in patients with functional dyspepsia. The involvement of CCK-A receptors was investigated by coadministering the specific CCK-A receptor antagonist dexloxiglumide.

Duodenal lipid caused a marked increase in gastric volumes compared with saline infusions. The symptomatic response to distension during lipid infusion was more pronounced in patients than in healthy controls while the gastric relaxatory effect was diminished in the patient group. Dexloxiglumide abolished the increase in gastric volume and reduced the severity of dyspeptic symptoms compared with placebo (fig 3).

These findings indicate that in patients with functional dyspepsia gastrointestinal symptoms induced by duodenal lipid and gastric distension can be relieved by the CCK-A receptor antagonist dexloxiglumide, suggesting that CCK-A receptors are involved in the induction of dyspeptic symptoms by fat.

CONCLUSION

The studies described herein sought to determine the role of nutrient fat and the postprandial release of CCK in the development of dyspeptic symptoms in healthy volunteers and in patients with functional dyspepsia. These studies have shown that during distension of the stomach, lipids are a major trigger of dyspeptic symptoms such as nausea, bloating, pain, and fullness, and that they modulate upper gastrointestinal sensations and symptoms in a dose related fashion. Hydrolysis of fat by lipases is a prerequisite for the effects of nutrient fat on postprandial gastrointestinal sensations and symptoms, including dyspepsia. Accordingly, indigestible fat has no effect on gastric perceptions during distension. Chemoreceptors in the small intestine are thought to be activated by the lipolytic products of fat: long chain fatty acids are probably the most important stimulus. These receptors can be blocked by the local anaesthetic agent benzocaine. CCK is a major mediator of the sensitisation of gastric perception by lipids in patients with functional dyspepsia, as the CCK-A receptor antagonist dexloxiglumide markedly diminishes this effect.

These findings provide insights into the mechanism of the modulation of upper gastrointestinal perception by nutrients and CCK in healthy subjects and in patients with functional dyspepsia. They also support the pathophysiological concept of functional dyspepsia and help to establish new therapeutic approaches for this common disorder, which includes a rationale for blockade of fat hydrolysis as well as a possible role for CCK-A antagonists. It also appears from these results that there is a rational basis for dietary counselling which may have design implications for future studies in functional dyspepsia.

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