Physiology and pathophysiology of the ileal brake in humans

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Chapter 1

INTRODUCTION, AIMS AND OUTLINES OF THE THESIS

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INTRODUCTION

Ileal brake history

Digestion and absorption of nutrients are complex processes that involve various functions of the gastrointestinal (GI) tract. This includes the interplay between nutrients, digestive enzymes and gut surface area. Motility, transport of intraluminal content, secretion of enzymes and fluids are regulated by hormonal, neural (enteric and central nervous system) and local regulatory mechanisms. Intraluminal nutrients by themselves have a major role in controlling gastrointestinal transport, digestion and absorption. The presence of nutrients in the small intestine stimulates pancreatic enzyme secretion, gallbladder contraction and converts intestinal motility from the fasted into a fed motility pattern (1). On the other hand, intestinal nutrients also trigger feedback inhibitory mechanisms that will modify gastrointestinal transport, digestion and absorption. For instance, duodenal nutrients inhibit gastric acid secretion and delay gastric emptying. This phenomenon is called the duodenal brake, a negative feedback loop from the proximal gut on gastric functions (1-3).

A nutrient-triggered inhibitory feedback loop from the more distal to the proximal gut was first described by Spiller et al and Read *et al* (4,5). These two groups of researchers showed that transit of a meal through the small intestine was significantly delayed when a lipid emulsion was administered into the ileum. This phenomenon is called the ileal brake. Since then, evidence has increased showing in both humans and animals that intraileal nutrients alter intestinal motility, reduce transit time, delay gastric emptying and inhibit gastric acid and exocrine pancreatic secretion (6-8,15-20,25-28).

One may conclude that non-absorbed nutrients reaching the distal small bowel bring the process of transport, secretion, digestion and absorption to an end.

1. Ileal brake and gastric emptying

Earlier studies in both humans and dogs have demonstrated that infusion of nutrients into the ileum delays gastric emptying of both solid and liquid meals (6,7). These findings have been further extended by Fone *et al*, who showed that ileal fat inhibits antral and duodenal motility while stimulating pyloric contractions. Especially the latter may be responsible for the delayed gastric emptying (8). However, this is the only study demonstrating an association between antropyloroduodenal motility changes and delayed gastric emptying induced by ileal nutrients in humans. Not only the distal stomach, but also the proximal stomach contributes to gastric emptying. The motor function of the proximal stomach is characterised by receptive and adaptive relaxation (9,10). Receptive relaxation is induced by pharyngeal stimulation (swallowing) and distention of the eosophagus by the bolus of food. Adaptive relaxation or accommodation is the ability of the proximal stomach to distend in response to an intragastric load with only minimal changes in intragastric pressure (gastric tone) (11). A relationship between proximal gastric tone and gastric emptying has been described previously (12-14). Up till now it is not known whether nutrients in the distal gut affect proximal gastric motor functions.

2. Ileal brake and intestinal motility and transit

The inhibitory effect of ileal nutrients on small intestinal transit has been

confirmed by several studies since the original publications of Spiller *et al* and Read *et al* (4,5,15,16). On the other hand, data on the effect of ileal nutrients on digestive intestinal motility patterns are scarce and the various studies differ in methodology. Welch *et al* demonstrated the early occurrence of phase III after meal ingestion in 3 of 14 healthy subjects by infusion of lipid into the ileum (17). A study by Layer *et al*, using duodenal perfusion of a mixture of essential amino acids instead of a meal to induce a fed-like motor pattern, showed that ileal infusion of fat or carbohydrate induces premature phase III-like activity in 12 of 14 healthy subjects (18). With respect to the effects of ileal nutrients on fasting motor patterns, results are contrasting. Ileal fatty acids in dogs prolong interdigestive cycles and inhibit jejunal motility (19) whereas in humans, ileal perfusion of carbohydrates or fat during interdigestive phase I markedly decreases the duration of phase II motor activity, induces premature phase III motility and shortens the length of the interdigestive cycle (20). Although contradictory, these results nonetheless suggest that fasting motor activities may be modulated by the presence of nutrients in the distal small intestine. However, further research is needed to exactly define the effect of ileal nutrients on intestinal motility patterns in humans.

3. Ileal brake and gastric acid and exocrine pancreatic secretion

It is known that nutrients in the proximal small intestine, especially fat, potently inhibit gastric acid secretion (21,22). However, there is also evidence suggesting that gastric acid secretory function is regulated by the distal intestine. For instance, colonic perfusion of lipids or protein decreases exogenously stimulated gastric acid secretion in humans and dogs (23, 24). In addition, ileal perfusion of lipids or carbohydrates inhibits both unstimulated and endogenously stimulated

gastric acid secretion in humans (25). The effects of ileal nutrients on the secretory function have been more extensively studied in humans and animals with respect to exocrine pancreatic secretion (26-28, 18, 20). However, the obtained results are contradictory. While in rats and cats, ileal fat decreases pancreatic enzyme secretion this is not the case in dogs (26-28). Layer et al showed in humans that ileal perfusion with either carbohydrates or triglycerides inhibits the secretion of all exocrine pancreatic enzymes to an equal extent (18). On the other hand, results presented by Jain *et al* indicate that ileal carbohydrates do not inhibit but increase the release of the pancreatic enzyme amylase when compared to trypsin (29). Thus, the question whether ileal nutrients inhibit exocrine pancreatic secretion still remains to be answered.

4. Ileal brake and satiety

Although the role of the stomach and intraduodenal nutrients in the regulation of food intake and satiety is well established (30-33), effects from the distal gut are poorly defined because of the limited number of studies on this subject up till now. There are two human studies, both by Welch *et al*, who have demonstrated that ileal nutrients significantly reduce the total amount of food intake (34, 35). In addition, one study in rats showed that while ileal infusion of glucose reduces both meal frequency and size, ileal free fatty acids reduce only the latter (36). Although scarce, these consistent data imply that activation of the ileal brake decreases food intake and may induce early satiety. However, further studies are necessary to prove this theory.

Triggers of the ileal brake

The ileal brake is an intraluminal nutrient-triggered feedback control from the distal to the proximal gut. The inhibitory response of upper gastrointestinal motility differs with respect to the type of the nutrients administered into the ileum. In both humans and dogs, infusion of fat into the ileum delays gastric emptying and increases intestinal transit time (4-8; 37, 38). Within the range of different lipid emulsions, free fatty acids and digested triglycerides have been shown to be more potent than neutral triglycerides in eliciting the ileal brake effect (15). Intraileal carbohydrates, on the other hand, delay gastric emptying only at high concentrations (15). Data concerning intraileal proteins and the activation of the ileal brake are contradictory. Read *at al* found that ileal proteins delay small intestinal transit (5) whereas other investigators were not able to demonstrate any inhibitory effects of ileal proteins on gastrointestinal motility in humans (6, 15). These contrasting data may result from methodological differences. Nevertheless, it is generally accepted, based on consistent results from numerous studies, that fat is the most potent trigger of the ileal brake (39). However, it is important to bear in mind that species differences exist concerning triggers for the ileal brake. For instance, free fatty acid, a potent trigger of the ileal brake in humans and dogs, has no effect on the pig (40).

Mediators of the ileal brake

The mechanisms involved in the control of the ileal brake remain to be explored. The ileal brake may be mediated by hormonal and/or neural factors.

Hormonal factors: A number of gut peptides, including glucagon-like peptide 1 (GLP-1), neurotensin and peptide YY (PYY) have been

hypothesized as possible humoral mediators of the ileal brake. Attention has been focused mainly on these peptides because of the localisation of their secretory cells, mainly in the distal gut.

GLP-1 is synthesized within the endocrine L cells in the intestine, primarily in the ileum and colon (41, 42). The release of GLP-1 is stimulated by the direct contact of the L cells to luminal nutrients (25, 43). However, given the rapid release of GLP-1 after meal intake, there is also evidence suggesting that GLP-1 release results from an indirect neural or humoral signals arising from the proximal gut (44, 45). GLP-1 plasma levels have been shown to increase in parallel with the inhibitory effects of the ileal brake on antral motility, gastric acid and exocrine pancreatic secretion (18, 25). However, up to now, there are no studies using a specific GLP-1 antagonist to clearly define the role of endogenous GLP-1 as a hormonal mediator of the ileal brake.

Neurotensin is produced by the mucosal endocrine N cells which are distributed throughout the small intestine, with the highest concentration found in the ileum (46-48). There is only scarce, indirect evidence available suggesting the role of neurotensin as a hormonal mediator of the ileal brake. Spiller *et al* have shown that ileal fat perfusion inhibits jejunal motility and significantly increases plasma neurotensin concentrations (5, 15).

PYY is, like GLP-1, also synthesized and secreted by L cells in the distal ileum and colon (49). The presence of nutrients, especially fats, in the ileum stimulates PYY release (4-8, 15). In contrast to the poorly established role of GLP-1 and neurotensin as hormonal mediators of the ileal brake, associations between plasma PYY concentrations and delayed small intestinal transit and gastric emptying have been shown by numerous investigators (5, 15, 37, 38).

In addition, the role of endogenous PYY as a mediator of the ileal brake has been elucidated using a PYY antagonist. In dogs, administration of PYY antibodies abolishes the prolonged small intestinal transit induced by intraileal fat (38). Although similar studies in humans are lacking, this direct evidence nonetheless suggests that PYY is very likely the humoral mediator of the ileal brake.

Neural factors: Several neural pathways have been suggested to contribute to the regulation of the ileal brake. The role of the extrinsic nervous system, in particular the vagus nerve, has been suggested but evidence is mostly indirect. It has been shown that intraileal fats increase vagal afferent activity in rats (50). In animals, the inhibitory effect of PYY and GLP-1 on meal stimulated gastric acid secretion and gastric motility was significantly reduced or even abolished after vagotomy (51, 52). These results suggest that both the candidate ileal brake hormones PYY and GLP-1 act through vagal innervation but a direct relationship between vagal cholinergic control and the fat induced ileal brake has not yet been proven. On the other hand, direct evidence exists demonstrating the involvement of the sympatho-adrenergic pathway in the inhibitory effect of the ileal brake. In dogs, administration of a combined α- and β-adrenergic blockade totally abolishes the inhibitory action of exogenous PYY en endogenous PYY release by ileal fat on exocrine pancreatic secretion (53). In addition, an adrenoceptor antagonist reverses the delayed intestinal transit induced by intraileal fat (54). Furthermore, evidence exists showing that the intrinsic nervous system (myenteric en submucosal plexus) also plays an important role the regulation of the ileal brake. The fat-induced ileal brake in dogs is abolished when ondansetron, a 5-HT3-receptor antagonist was administered into the proximal but not the distal small bowel

(55). Similarly, the prolonged intestinal transit induced by fat in the ileum was blocked when naloxon, an opioid receptor antagonist was infused into the proximal small intestine (56). These findings suggest that both peripheral serotonergic and also opioid pathways are involved in the regulation of the ileal brake. However, it is plausible to assume that all the abovementioned different neural pathways interact and regulate the ileal brake.

Clinical implications of altered ileal brake function

Theoretically, the feedback function of the ileal brake could be impaired due to mucosal defects as in Crohn's ileitis and celiac disease or could be absent following resection of the distal small intestine. It is plausible to hypothesize that when the inhibitory feedback mechanism of the ileal brake is impaired or absent, gastric emptying and small intestinal transit are accelerated, resulting in increased concentrations of undigested and unabsorbed nutrients in the distal gut. This in turn could contribute to the development of symptoms such as diarrhea and malabsorption seen in inflammatory bowel diseases and after small intestine resection.

On the other hand, malabsorption and/or accelerated intestinal transit, irrespective of its cause, may also alter the ileal brake function. Given that PYY is a candidate hormonal mediator of the ileal brake, plasma PYY release could be considered as a marker for the activation of this feedback mechanism. Plasma PYY levels have been found to be increased in chronic pancreatitis and in patients with dumping syndrome after (partial) gastric resection (57-59). These findings suggest that the activation of the ileal brake is enhanced in these disease states due to the increased amount of unabsorbed nutrients reaching the distal small intestine. Based on the above made

assumptions, altered ileal brake function could be a primary defect, thereby giving rise to disease manifestations or secondary, in response to changes caused by the disease.

AIMS AND OUTLINES OF THE THESIS

Given its important role as a nutrient-triggered feedback control mechanism, increasing knowledge and understanding of the ileal brake is relevant for physiology and pathophysiology and may help to develop novel strategies in treating patients with malabsorption and maldigestion. The studies presented in this thesis have been designed to gain further insight into the physiology and pathophysiology of the ileal brake. The following issues were addressed:

Physiology of the ileal brake

- It has been shown in dogs that the ileal brake is a more potent feedback mechanism compared to the more proximal, so called jejunal brake. However, a comparative study between jejunal and ileal brake has not been performed in humans. **Chapter II** was therefore designed to compare the effect of intraileal versus intrajejunal fat on digestive and interdigestive gastrointestinal motor patterns and postprandial gallbladder motility. The latter plays a role in delivering bile acids into the duodenum for the digestion of dietery fats. Furthermore, impaired gallbladder motility contributes to the pathogenesis of sludge and stone formation. Up til now little is known about the effect of the ileal brake on gallbladder motility. Gallbladder volumes were measured by real time ultrasonography and gastrointestinal motility was measured by means of the stationary water perfusion manometry system.

- The study in C**hapter III** was designed to investigate whether pancreatic and biliary secretion will be affected when nutrients are administered more distally into the small intestine than usual during enteral feeding. Duodenal outputs of pancreatic enzymes and bilirubin were measured by aspiration using a recovery marker in healthy volunteers.
- It has been shown in recent years that the distal gut hormone PYY has an important role in satiety and eating behaviour. However, little is known about the effect of the ileal brake on satiety and proximal gastric motor function. **Chapter IV** was undertaken to compare the effects of ileal brake activation with ileal fat (endogenous PYY release) versus exogenous PYY_{3-36} infusion on satiety and on proximal gastric motor function. Two experimental protocols were used. In the first protocol, the effect of ileal fat and subsequent endogenous PYY release was studied and in the second protocol, the dose-response relationship of exogenous PYY was investigated. In both protocols satiety and motor function of the proximal stomach were monitored using Visual Analog Scale (VAS) and an electronic barostat, respectively. Plasma PYY levels were measured by radioimmunoassay.
- Medium chain triglycerides (MCT) are thought to be hydrolysed and absorbed more rapidly and completely compared to long chain triglycerides (LCT). However, patients receiving MCT frequently complain of nausea, cramps, abdominal pain and diarrhoea. We hypothesized that MCT are less rapidly absorbed and cause these gastrointestinal side effects. The release of the distal gut hormone PYY induced by intraduodenal MCT was used as evidence for the hypothesized malabsorption of MCT. Results are described in **Chapter V.**

- **Chapter VI** investigates whether artificially induced malabsorption in healthy volunteers affects gastrointestinal and gallbladder motility through activation of the ileal brake. The osmotic laxative magnesium sulphate was used to induce malabsorption after ingestion of a fatty meal.

Pathophysiology of the ileal brake

- Altered gastrointestinal motility has been observed in patients with chronic pancreatitis with impaired exocrine function. However, the reported results are conflicting. In **Chapter VII** we therefore investigated digestive and interdigestive antroduodenal motility and secretion of several relevant gut hormones in a large group of patients with chronic pancreatitis. Differences in gut motility and hormone secretion were compared between patients with and without exocrine pancreatic insufficiency. Gastrointestinal motility and hormone secretion were also studied after pancreatic enzyme supplementation in order to further elucidate the role of exocrine pancreatic insufficiency and subsequent maldigestion in patient with chronic pancreatitis
- **Chapter VIII** deals with patients with systemic sclerosis. This systemic disorder may give rise to various complications within the gastrointestinal tract. In this chapter we focused on antroduodenojejunal motility and proximal and distal gut hormone release in patients with diffuse and limited type of systemic sclerosis. The obtained data were related to esophageal manometry findings and gastrointestinal symptoms.
- It is known that patients with Crohn's disease have an increased risk of developing gallstones. When considering the possible mechanisms that contribute to gallstone formation in these patients the questions are: 1)

whether gallbladder motility plays a role in the pathogenesis of gallstone formation in Crohn's disease and 2) whether changes in gallbladder motility are explained by altered ileal brake function due to disease localization and bowel resection. These items have been investigated and results are described in **chapter IX**.

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