Resection and palliation of pancreatic and periampullary carcinoma
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CHAPTER 8

Effect of pancreatic surgery on proximal and distal gut hormone secretion.

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Submitted
Abstract

**Background:** In patients with chronic pancreatitis (CP) the relation between exocrine pancreatic secretion and gastrointestinal hormone release is disturbed. Little is known of the influence of different surgical procedures for pancreatic disease on gastrointestinal hormone release. The aim of this study was evaluate hormone secretion after two types of pancreatic surgery, pylorus preserving pancreaticoduodenectomy (PPPD) and duodenum preserving resection of the head of the pancreas (DPRHP).

**Methods:** We studied secretion of a proximal and a distal gut hormone (CCK and PYY, respectively) in response to a meal in patients after PPPD (n=22), DPRHP (n=9), non-surgically treated CP patients (n=12), and healthy controls (n=14).

**Results:** Basal plasma CCK levels were not significantly different between the groups. Postprandially an increase in plasma levels was seen in all groups. The postprandial peak increment in plasma CCK in patients after PPPD (0.6 ± 0.1 pmol/l) was significantly lower compared to that in patients after DPRHP (1.7 ± 0.3 pmol/l; p<0.01), and non-operated CP patients (1.5 ± 0.2; p<0.01). The integrated plasma CCK secretion in patients after PPPD (25 ± 6 pmol/l ·120 min) was also significantly lower compared to the integrated plasma CCK secretion in patients after DPRHP (86 ± 32 pmol/l ·120 min; p<0.05), and non-operated CP patients (84 ± 17 pmol/l ·120 min; p<0.01). Basal plasma PYY level in patients after PPPD (35.3 ± 2.2 pmol/l) was significantly higher compared to patients after DPRHP (23.7 ± 2.6 pmol/l; p=0.01), and non-operated CP patients (22.9 ± 1.3 pmol/l; p<0.01). In all groups a significant postprandial increase in plasma levels occurred. The peak increment and integrated plasma PYY secretion in the PPPD group was not significantly different from that in the DPRHP or the CP group.

**Conclusions:** In CP patients proximal hormone secretion is decreased and distal hormone secretion is increased compared to healthy controls. After pancreatic surgery without resection of the duodenum no significant changes in proximal or distal hormone secretion compared to CP patients were found, whereas after PPPD proximal hormone secretion was decreased and distal hormone secretion was increased.
Effect of pancreatic surgery on proximal and distal gut hormone secretion

Introduction
Pylorus preserving pancreaticoduodenectomy (PPPD) is performed for malignant or benign diseases of the pancreas. After resection patients frequently suffer from exocrine pancreatic insufficiency that does not always sufficiently respond to enzyme supplementation. Resection may interfere with the complex mechanisms that regulate nutrient digestion such as gastrointestinal motility and hormone secretion. Under normal conditions, after meal ingestion gastrointestinal motility is converted from a fasting into a feeding pattern and exocrine pancreatic secretion increases. The control of interdigestive and digestive motility and pancreatic secretion includes neural and hormonal components. Cholecystokinin (CCK), a proximal gut hormone, acts as a regulator of gallbladder contraction, pancreatic exocrine secretion and intestinal motility, and is released mainly from endocrine cells in the duodenum and proximal jejunum. Therefore, when pancreatic surgery is performed with resection of the duodenum, such as classical Whipple’s procedure or PPPD, changes in CCK secretion can occur.

Non-operated chronic pancreatitis (CP) patients who suffer from exocrine pancreatic insufficiency have reduced postprandial release of CCK due to impaired intraluminal enzyme activity to digest fat. Only fat digest products are able to release CCK. Apart from drainage procedures, surgical treatment of CP patients consist mainly of PPPD or duodenum preserving resection of the head of the pancreas (DPRHP), in which the duodenum remains in situ but the pancreas drainage is diverted via a pancreaticojejunostomy. It is unclear whether pancreatic surgery with or without resection of the duodenum will have a different effect on postprandial CCK release.

PYY, a distal gut hormone, is found in highest concentrations in the mucosa of the distal gut, and is considered one of the mediators of the so-called ileal brake. In patients with exocrine pancreatic insufficiency, PYY levels are increased. It is unclear whether pancreatic surgery will affect the ileal brake.

This study was undertaken to evaluate the effect of pancreatic surgery on proximal and distal postprandial gastrointestinal hormone release in patients after different types of pancreatic surgery with impaired exocrine pancreatic function.

Methods
Subjects
Postprandial release of the proximal gut hormone cholecystokinin (CCK) and of the distal gut hormone peptide YY (PYY) were compared in four groups: 1) pylorus preserving pancreaticoduodenectomy (PPPD) (n=22), either for ampullary carcinoma (n=12) or chronic pancreatitis (n=10); 2) duodenum preserving resection of the head of the pancreas (DPRHP) for CP in 9 patients; 3) 12 non-surgically treated CP patients with exocrine pancreatic insufficiency; 4) 14 healthy controls (table 1). The median time after surgery was 3.5 ± 0.3 years for the PPPD group and 2.9 ± 0.6 years for the DPRHP group.

The diagnosis of CP had been established in all patients by the typical clinical history and characteristic abnormalities on ultrasonography, computed tomography, or endoscopic retrograde cholangiopancreatography. At the time of the study, none of the patients that underwent PPPD for malignant disease had any sign of tumour recurrence. Exocrine
pancreatic function was assessed by the indirect para-aminobenzoic acid (PABA) test and faecal fat excretion. Impaired exocrine pancreatic function was defined as a urinary PABA recovery of <50% and/or faecal fat excretion of >7 g/24 h. Pancreatic enzyme supplementation and other medication possibly interfering with hormone secretion or motility were discontinued at least 4 days before the study.

**Study Design**

After an overnight fast, patients received a standard solid fat meal that consisted of 1 hamburger, 1 slice of bread, 25 g of margarine, mayonnaise and 150 ml tea at 2.00 PM. The meal contained 10 g protein, 40 g fat and 22 g carbohydrates (500 kcal). Blood samples for measurement of plasma CCK and PYY were drawn at 10 and 0 min before meal ingestion, and after the meal at 10, 20, 30, 45, 60, 75, 90, 105, and 120 minutes. Plasma CCK was measured by a sensitive and specific radioimmunoassay. This antibody binds to all CCK peptides, including sulphated CCK octapeptide, but not with gastrin. The detection limit of the assay is 0.3 pmol/l plasma. The intra-assay variation ranges from 4.6 to 11.5% and the inter-assay variation from 11.3 to 26.1%\textsuperscript{15}. Plasma PYY was measured by a radioimmunoassay. PYY antiserum was generated in rabbits by intracutaneous injections of synthetic human PYY (Bachem Biochemica). PYY was labeled with \textsuperscript{125}I with chloramine T. The assay is highly specific. There is no cross-reactivity with PP or VIP. The detection limit is 10 pmol/l. Both PYY-(1-36) and PYY-(3-36) bind to the antibody in dilutions up to 1:250,000\textsuperscript{10}.

**Data and Statistical Analysis**

Results are expressed as mean ± SEM. Integrated incremental CCK and PYY secretion in response to the meal were determined by calculating the area under the plasma concentration time curve after subtraction of the basal value at 0 min. Statistical analysis of basal, peak increment and integrated CCK and PYY values between groups was performed by Mann-Whitney test. To identify differences within groups, repeated measures of variance was used in a general linear model. Statistical significance was defined as a P value <0.05.

**Results**

**Exocrine function**

There were no significant differences in PABA recovery or 24 hour faecal fat excretion between the different patient groups (table 1). All patients had an exocrine pancreatic insufficiency.

**Plasma CCK**

Basal plasma CCK levels in patients after PPPD (1.4 ± 0.1 pmol/l), DPRHP (2.2 ± 0.4 pmol/l), CP (1.3 ± 0.2 pmol/l), and healthy controls (1.3 ± 0.2 pmol/l) did not differ significantly (Table 2). After ingestion of the meal plasma CCK levels increased significantly over basal starting from 10 minutes in the control (p=0.001) and the DPRHP group (p=0.005), and from 20 minutes in the CP (p=0.001) and PPPD group (p=0.012) (Figure 1).
Effect of pancreatic surgery on proximal and distal gut hormone secretion

Table 1. Number of patients, gender, mean age, mean PABA recovery (%) and mean 24 hour faecal fat excretion (g/24h) in healthy controls (HC), in non-operated chronic pancreatitis patients (CP), in patients after duodenum preserving resection of the head of the pancreas (DPRHP), and in patients after pylorus preserving pancreaticoduodenectomy (PPPD).

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>CP</th>
<th>DPRHP</th>
<th>PPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>12</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Male / female</td>
<td>9 / 5</td>
<td>9 / 3</td>
<td>8 / 1</td>
<td>17 / 5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 ± 5</td>
<td>48 ± 2</td>
<td>46 ± 3</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PABA recovery</td>
<td>65 ± 7</td>
<td>27 ± 6</td>
<td>31 ± 6</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Faecal fat</td>
<td>4 ± 1</td>
<td>32 ± 8</td>
<td>24 ± 6</td>
<td>26 ± 8</td>
</tr>
</tbody>
</table>

Table 2. Results of basal and postprandial CCK and PYY plasma levels in healthy controls (HC), in non-operated chronic pancreatitis patients (CP), in patients after duodenum preserving resection of the head of the pancreas (DPRHP), and in patients after pylorus preserving pancreaticoduodenectomy (PPPD).

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>CP</th>
<th>DPRHP</th>
<th>PPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal plasma levels</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>2.2 ± 0.4</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Integrated CCK secretion</td>
<td>170 ± 15</td>
<td>84 ± 17 †</td>
<td>86 ± 32</td>
<td>25 ± 6 †</td>
</tr>
<tr>
<td>Postprandial peak increments</td>
<td>2.4 ± 0.1</td>
<td>1.5 ± 0.2 †</td>
<td>1.7 ± 0.3</td>
<td>0.6 ± 0.1 †</td>
</tr>
<tr>
<td>PYY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal plasma levels</td>
<td>17.9 ± 1.0</td>
<td>22.9 ± 1.3 †</td>
<td>23.7 ± 2.6</td>
<td>35.3 ± 2.3 †</td>
</tr>
<tr>
<td>Integrated PYY secretion</td>
<td>612 ± 92</td>
<td>1141 ± 279</td>
<td>764 ± 313</td>
<td>963 ± 217</td>
</tr>
<tr>
<td>Postprandial peak increments</td>
<td>8.9 ± 0.9</td>
<td>14.0 ± 2.8</td>
<td>11.0 ± 3.0</td>
<td>20.5 ± 3.9</td>
</tr>
</tbody>
</table>

*p<0.05 compared to HC, †p<0.05 compared to CP, ‡p<0.05 compared to DPRHP

The peak increment in plasma CCK in patients after PPPD (0.6 ± 0.1 pmol/l) was significantly lower compared to the peak CCK increment in patients after DPRHP (1.7 ± 0.3 pmol/l; p<0.01), non-operated CP patients (1.5 ± 0.2 pmol/l; p<0.01), and healthy controls (2.4 ± 0.1; p<0.01) (Figure 2). The integrated plasma CCK secretion in patients after PPPD (25 ± 6 pmol/l ·120 min) was also significantly lower compared to the integrated plasma CCK secretion in patients after DPRHP (86 ± 12 pmol/l ·120 min; p<0.05), non-operated CP patients (84 ± 17 pmol/l ·120 min; p<0.01), and healthy controls (170 ± 15 pmol/l ·120 min; p<0.01). There were no significant differences between patients that underwent PPPD for chronic pancreatitis or for malignant disease in basal CCK secretion (1.4 ± 0.1 pmol/l and 1.4 ± 0.1 pmol/l, respectively; p=0.44), peak increment in plasma CCK (0.6 ± 0.1 pmol/l and 0.5 ± 0.1 pmol/l, respectively; p=0.92), or integrated plasma CCK secretion ( 29.0 ± 8.1 pmol/l ·120 min and 22.4 ± 9.4 pmol/l ·120 min, respectively; p=0.74).
Figure 1. Basal and postprandial plasma levels CCK levels (means ± SEM) in patients after pylorus preserving pancreaticoduodenectomy (PPPD), duodenum preserving resection of the head of the pancreas (DPRHP), non-operated chronic pancreatitis (CP), and healthy controls (HC).

Figure 2. Individual data of postprandial peak increments in plasma CCK (pmol/L) after ingestion of a solid fat meal in patients after pylorus preserving pancreaticoduodenectomy (PPPD), duodenum preserving resection of the head of the pancreas (DPRHP), non-operated chronic pancreatitis (CP), and healthy controls (HC).
Effect of pancreatic surgery on proximal and distal gut hormone secretion

**Plasma PYY**

Basal plasma PYY levels in patients after PPPD (35.3 ± 2.2 pmol/l) was significantly higher compared to patients after DPRHP (23.7 ± 2.6 pmol/l; p=0.01), non-operated CP patients (22.9 ± 1.3 pmol/l; p<0.01), and healthy controls (17.9 ± 1.0 pmol/l; p<0.01) (Table 2). After ingestion of the meal plasma PYY levels increased significantly over basal starting from 15 minutes in the controls (p=0.012), CP (p=0.021) and DPRHP (p=0.006), and from 30 minutes in the PPPD (p=0.006) (Figure 3). The peak increment of plasma PYY in the PPPD group was not significantly different from that in the DPRHP group or the CP group. The integrated plasma levels of PYY did not differ significantly between the groups. There were no significant differences in PYY secretion between patients that underwent PPPD for chronic pancreatitis or for malignant disease.

![Figure 3](image-url)

**Figure 3.** Basal and postprandial plasma levels PYY levels (means ± SEM) in patients after pylorus preserving pancreaticoduodenectomy (PPPD), duodenum preserving resection of the head of the pancreas (DPRHP), non-operated chronic pancreatitis (CP), and healthy controls (HC).

**Discussion**

This study demonstrates that postprandial CCK secretion is significantly reduced in patients with CP compared to healthy controls. After PPPD but not after DPRHP postprandial CCK secretion was significantly reduced compared to CP although the degree of exocrine pancreatic insufficiency was comparable.

The finding of a reduced CCK secretion in CP patients is inline with previous studies. Several mechanisms may be responsible. Firstly, reduction in CCK release may be caused by
delayed gastric emptying after the meal. However, in CP patients gastric emptying is not delayed, but in the normal range or even accelerated. Secondly, a reduced capacity of CCK secreting cells can be excluded since CCK release in response to bombesin is not reduced in CP patients. A more likely explanation for the reduced CCK secretion is related to the observation that CCK release is dependent on the digestion of nutrients. Fat and proteins need to be digested by pancreatic enzymes to fatty acids and monoglycerides or oligopeptides and amino acids in order to be able to release CCK. It has also been shown that a reduced postprandial CCK secretion in CP patients can be normalised by increasing intraluminal pancreatic enzyme activity by administration of exogenous enzymes.

In patients after DPRHP, basal CCK levels were even elevated when compared to CP and PPPD patients, although this difference was not significant. Basal plasma CCK levels are regulated by feedback of pancreaticobiliary secretion. Therefore, bile deviation may increase basal plasma CCK levels. Because of the pancreaticojunostomy in DPRHP the duodenum is devoid of pancreatic enzymes. Pancreatic enzymes also exert an inhibitory effect on CCK release. This may explain the higher basal CCK levels in patients after DPRHP.

In patients after PPPD basal plasma CCK levels were not different from CP patients. Integrated postprandial CCK secretion and peak increments in CCK were significantly lower compared to CP patients but also to DPRHP patients. This is in line with previous findings of a decreased CCK response in PPPD patients after a fatty liquid meal or solid meal in comparison to healthy controls or DPRHP, respectively. Since the degree of exocrine insufficiency was comparable between DPRHP and PPPD patients we believe that this finding can be explained by the resection of the duodenum, leading to a reduction in CCK secreting capacity. Still, other factors might also contribute to the decreased CCK levels. Delayed gastric emptying occurs in about 30% of the patients after PPPD and may lead to a reduction in CCK secretion in the early postprandial period.

In PPPD patients the proximal rim of the duodenum that contains the duodenal pacemaker remains in situ to preserve pylorus-duodenal co-ordination. However, there are no significant differences in the prevalence of delayed gastric emptying between patients after PPPD or a classical Whipple’s procedure in which the duodenum and pylorus are both resected. In our study PPPD patients were studied after a mean period of 3.5 ± 0.3 years after the operation, whereas others described an only temporary reduction in CCK secretion in the postoperative period that recovered after six months. Unfortunately, in that study it was not reported whether patients had exocrine insufficiency or were supplemented with enzymes at six months.

Basal PYY plasma levels in all patients groups were higher compared to controls, although this difference did not reach statistical significance in the DPRHP group. PYY is found in highest concentrations in the mucosa of the distal gut and is considered to be one of the mediators of the so-called ileal brake. In the present study, PYY was chosen as a marker of the ileal brake because there is substantial evidence suggesting that plasma PYY levels correlate with ileal activation of the ileal brake. PYY levels increase with fat-induced delayed gastric emptying, prolonged small intestinal transit, and inhibition of small intestinal motility. The basal PYY plasma levels of patients after PPPD were significantly higher compared to those with CP or DPRHP, which points to an increased activation of the ileal brake. Elevated plasma PYY levels have been found in diseases associated with
malabsorption such as celiac sprue, cystic fibrosis, dumping syndrome, and exocrine pancreatic insufficiency\textsuperscript{10, 29-31}. These findings support the idea that alterations in plasma PYY secretion in patients with pancreatic insufficiency result from malabsorption. Ingestion of pancreatic enzymes before the meal improve digestion and absorption in chronic pancreatitis and is associated with a reduction in PYY secretion\textsuperscript{10}. The presence of undigested and unabsorbed nutrients in the distal gut activates the ileal brake with concomitant PYY release. The physiological relevance is a feedback regulation of proximal gut motor and secretory function in order to optimise nutrient uptake and absorption.

References


