Case report

Two patients with pancreatic apudomas secreting neurotensin and VIP

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SUMMARY Two patients have been studied with a two and a half and nine year history of metastatic pancreatic apudoma. In both patients the main feature was chronic watery diarrhoea with remissions after partial tumour resection and streptozotocin therapy. Plasma levels of circulating VIP and neurotensin were persistently raised in both patients. Chromatographic analysis of the plasma showed that a significant proportion of the raised immunoreactivity of both peptides eluted in an identical position to pure VIP and neurotensin. The extremely high concentrations of neurotensin did not appear to result in any feature which would allow distinction from the classical VIPoma syndrome.

Neurotensin is a 13 amino acid polypeptide first extracted from bovine brain by Carraway and Leeman. It has been subsequently isolated from the human gastrointestinal tract and found to have the same amino acid sequence. Neurotensin has a number of potent pharmacological actions including production of hypotension, tachycardia, and cyanosis and also small intestinal juice production. When infused in man in amounts to exceed the concentrations seen postprandially, however, no effect on the cardiovascular system was noted but an inhibition of gastric emptying, gastric acid secretion, and stimulation of pancreatic bicarbonate juice production occurred. Neurotensin has also been reported to inhibit the interdigestive myoelectric complex and stimulate insulin release. Its physiological role is at present unknown.

Pancreatic VIPomas have been shown to be associated with severe watery diarrhoea and hypokalaemia. Approximately half the cases have hepatic metastases at the time of diagnosis. These tumours often contain mixed cellular elements and, in particular, approximately three-quarters of them secrete, in addition, pancreatic polypeptide. The previous finding that neurotensin production could occasionally occur in VIPomas, and result in raised blood levels, prompted us to screen all patients investigated over the last year for additional production of neurotensin. Only two patients were identified with high plasma neurotensin concentrations. Very surprisingly both attended the Hopital de Hautepierre in Strasbourg and are, therefore, reported here together.

Case 1

A 49 year old man (weighing 73 kg) presented with persistent watery diarrhoea (1–3 litres/day), weight loss (5 kg) and hypokalaemic acidosis (mean K⁺ 2.7 mmol/l, bicarbonate 14 mmol/l plasma) but normal plasma calcium and no steatorrhea. Endoscopic retrograde pancreatography showed ductal block. The presence of a tumour in the pancreatic tail and numerous small hepatic metastases was shown by arteriography. Pentagastrin-stimulated gastric acid secretion was within the normal range and oral glucose tolerance was also normal.

In view of the persistent symptoms, the patient underwent partial pancreatectomy with removal of the tumour mass. Postoperatively intravenous streptozotocin was administered to a total of 6 grams. Stool volume subsequently fell to a mean
of 350 ml per day but remained of liquid consistency. The patient felt very much better and regained the 5 kg in weight. Histology showed the tumour to be of endocrine type with cells of non-alpha and non-beta cell pattern. Electron microscopy showed small electron-dense granules characteristic of the VIPoma pattern. Subsequently an ultrasound showed further enlargement of the hepatic metastases and another course of streptozotocin (9 g) was administered. Unfortunately heavy proteinurea resulted (10 g/24 h). A course of 5 fluorouracil (500 mg/day for five days a month for three months) was without apparent effect on symptoms or tumour mass. Currently the patient remains unwell with a loss of weight of 15 kg owing to hyperthyroidism.

Case 2

A 27 year old woman (weighing 64 kg) presented in 1972 with 10 kg weight loss and persistent watery diarrhoea (1-1 litres daily). This was resistant to all therapy and two years later a laparotomy was performed. A tumour weighing 600 g was resected from the tail of the pancreas but no visible metastases were shown. Histology showed non-beta cell endocrine tumour. Postoperatively the patient felt completely well but hypercalcaemia (2.7-2.85 mmol/l) and hyperglycaemia (mean fasting blood glucose 7.5 mmol/l) were noted. She remained in reasonable health until in 1979 the diarrhoea returned. At this time she was noted to have a stool volume of 1-4 litres per day, hypokalaemia (2.4 mmol/l), hypercalcaemia (3.0 mmol/l) and hyperglycaemia (fasting glucose 7.8 mmol/l). Neck exploration was performed and both inferior parathyroid glands were removed. Subsequent histology suggested gland hyperplasia. Calcium fell temporarily to normal and then rose again to 3.1 mmol/l. The diarrhoea and hypokalaemia continued. Pentagastrin-stimulated gastric acid secretion was on three occasions within the normal range. Upper abdominal ultrasound, coeliac axis arteriography and ERCP revealed the presence of a tumour in the head of the pancreas and numerous hepatic metastases. Intravenous streptozotocin was administered in a total of 16 g over two months. Stool volume, plasma potassium, plasma calcium, and plasma glucose returned completely to normal. The urine protein excretion, however, rose to 1 g per 24 hours. One year later a further course of streptozotocin (9 g) was instigated without any improvement. Unfortunately proteinurea increased to 5 g per 24 hours, though 10 months later it had returned to 0.3 g per 24 hours again. Blood urea and creatinine remained within the normal range. The patient currently complains of tiring easily, but has significant hyperglycaemia. The calcium remains normal.

**PLASMA HORMONE MEASUREMENTS**

Plasma gastrin, pancreas polypeptide, neurotensin, somatostatin, VIP and pancreatic glucagon were measured by radioimmunoassay. The assay for plasma neurotensin was C-terminally directed and does not detect the biologically inactive N-terminal fragments - that is, NT 1-8. The initial hormone concentrations for both patients are given in the Table. VIP and neurotensin were found to be grossly raised, while pancreatic polypeptide was above the normal range in only one patient and not greatly raised. The effects of cytotoxic therapy are shown in Figures 1a and 1b. In both cases the nature of the immunoreactivity was analysed by direct chromatography of the plasma by gel permeation (G50 Sephadex). The profiles (Figures 2a, 2b and 2c) show that the majority of the immunoreactive materials for all three hormones estimated eluted in the position of the pure hormone markers. Parathyroid hormone was measured in case 2 and was found to be 1.48 ng/ml (normal range 0.37-2.22 ng/ml).

**Discussion**

Neurotensin, a newly discovered regulatory peptide, is present in both brain and peripheral tissues. High concentrations are present in the ileal mucosa where it is localised to a specific endocrine cell. Plasma concentrations rise after food but physiological

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**Table Initial hormone concentrations (pmol/l)**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gastrin</th>
<th>Pancreatic polypeptide</th>
<th>Neurotensin</th>
<th>Vasoactive intestinal polypeptide</th>
<th>Somatostatin</th>
<th>Pancreatic glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>&lt; 5</td>
<td>173</td>
<td>4225</td>
<td>98</td>
<td>&lt; 2</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Case 2</td>
<td>&lt; 5</td>
<td>760</td>
<td>3700</td>
<td>110</td>
<td>&lt; 2</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Upper limit of normal in healthy controls</td>
<td>&lt;40</td>
<td>&lt;200</td>
<td>&lt;100</td>
<td>&lt;30</td>
<td>&lt;50</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>
Fig. 1a  Plasma levels of neurotensin (NT), vasoactive intestinal polypeptide (VIP) and pancreatic polypeptide (PP) from case 1 over period of two years. Double arrows indicate administration of streptozotocin (6 g and 9 g respectively).

Fig. 1b  Plasma levels of neurotensin (NT), vasoactive intestinal polypeptide (VIP) and pancreatic polypeptide (PP) from case 2 over period of two years. Double arrows indicate administration of streptozotocin (16 g and 9 g respectively).

The role of circulating neurotensin is at present unknown. High concentrations have been reported in patients after surgery for the treatment of duodenal ulcer and jejuno-ileal bypass for obesity. In addition a recent series of six patients with VIPoma were found to have raised plasma neurotensin concentrations (highest 860 pmol/l). A further case also produced several hormones. The neurotensin concentrations found in the plasma of the two patients reported here are an order of magnitude higher than any previously recorded. This neurotensin-like immunoreactivity was indistinguishable on chromatographic analysis from pure synthetic neurotensin. Unfortunately both tumours were also secreting VIP. The main clinical features of the patients appeared to fit well with those previously recorded for the VIPoma syndrome alone without additional secretion of neurotensin. Thus there appeared to be no feature specific for the extremely high plasma neurotensin concentration. In particular, case 2 is in reasonably normal health in spite of plasma neurotensin concentrations which may be as much as a hundred-fold increased over the normal resting fasting level. As it is not possible to perform a bioassay, it is conceivable that the neurotensin secreted is inactive, though it behaves similarly in its chromatographic characteristics to active neurotensin. Alternatively, the symptoms of neurotensin may be similar to those of VIP and thus difficult to distinguish in tumours secreting both peptides. Perhaps the most likely explanation for the lack of specific features, however, is that with long continued elevation, escape from the effects of neurotensin can occur. We await the discovery of a tumour secreting only neurotensin to help clarify these matters.
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![Graphs showing gel permeation chromatographic profiles of plasma neurotensin from case 1 (upper profile) and case 2 (lower profile) on Sephadex G-50 superfine. The column was calibrated with dextran blue (Vo), cytochrome C (CC), $^{125}$I labelled neurotensin and Na$^{25}$I (V$_t$) as molecular size markers. Fractions of 0.7 ml were eluted with 0.06M phosphate buffer, pH 7.2 containing 1% human serum albumin.](Fig. 2a)

![Graphs showing gel permeation chromatographic profiles of plasma vasoactive intestinal polypeptide (VIP) from case 1 (upper profile) and case 2 (lower profile) on Sephadex G-50 superfine. The 0.9x60 cm column was calibrated with dextran blue (Vo), cytochrome C (CC), $^{125}$I labelled VIP and Na$^{25}$I (V$_t$) as molecular size markers. Fractions of 0.7 ml were eluted with 0.06M phosphate buffer, pH 7.2 containing 1% human serum albumin.](Fig. 2b)

![Graphs showing gel permeation chromatographic profiles of plasma pancreatic polypeptide (PP) from Case 2 in Sephadex G-50 superfine. The 0.9x60 cm column was calibrated with dextran blue (Vo), cytochrome C (CC), $^{125}$I labelled PP and Na$^{25}$I (V$_t$) as molecular size markers. Fractions of 0.7 ml were eluted with 0.06M phosphate buffer, pH 7.2 containing 1% human serum albumin.](Fig. 2c)
References

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