Elevation of plasma neurotensin in the dumping syndrome


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Summary

1. The pathophysiology of the dumping syndrome is poorly understood. Plasma levels of four small intestinal hormones have been measured after an oral glucose provocation test in 19 patients with dumping symptoms and in matched controls.

2. Plasma levels of neurotensin, a newly discovered highly potent, hypotensive ileal peptide, were significantly increased in symptomatic patients compared with those of controls [20 min rise of 43 ± 6.0 (mean ± SEM) pmol/l in 19 symptomatic patients, 8.0 ± 5.5 pmol/l in 20 postoperative symptom-free patients, and 4.1 ± 3.5 pmol/l in 20 pre-operative patients with duodenal ulcer, P < 0.01].

3. The rise in enteroglucagon was greater than normal but of similar magnitude to that seen in several other gastrointestinal conditions not associated with dumping symptoms.

4. The release of both gastric inhibitory peptide and motilin did not differ significantly from that of controls.

Key words: dumping syndrome, enteroglucagon, gastric inhibitory peptide, motilin, neurotensin.

Introduction

The dumping syndrome (Meurling, 1953) affects a small but significant proportion of people after all forms of gastric surgery for peptic ulceration (Humphrey, Johnston, Walker, Pulvertaft & Goligher, 1972). A number of possible aetiological factors have been suggested, of which the well-established rapid emptying of liquids from the stomach may be the single most important. This results in the sudden arrival of a large volume of hyperosmolar fluid into the small intestine causing an osmotic shift of plasma fluid into the bowel lumen, a fall in circulating plasma volume and consequent haemoconcentration (Le Quesne, Hobsley & Hand, 1960). In 1961, Johnson & Jesseph postulated that a hormonal factor was responsible for the dumping syndrome and, since then, various candidates such as serotonin (Peskin & Miller, 1962) and bradykinin (Zeitlin & Smith, 1966) have been proposed. However, none of these factors has yet adequately explained the complex pathophysiology of this syndrome.

We investigated the release of four possible candidates for the hormonal factor involved in dumping. They are peptide hormones localized in the lining mucosa of the small intestine: gastric inhibitory peptide (or glucose-dependent insulino trophic peptide) and motilin, found proximally, and enteroglucagon and neurotensin, found distally in the small intestine. Neurotensin, a tridecapeptide originally discovered in the brain (Carraway & Leeman, 1973), is present in greatest quantities in the gastrointestinal tract (Carraway & Leeman, 1976). In man it is found mainly in the ileum, where it is produced by specific endocrine cells in the mucosa (Polak, Sullivan, Bloom, Buchan, Facer, Brown & Pearse, 1978). Neurotensin is a highly vasoactive substance being originally classed with the kinins (Carraway & Leeman, 1973). In experimental animals, bovine neurotensin produces marked hypotension, elevates packed cell volume...
immunoreactivity was investigated in a group of patients who had undergone surgery for treatment of duodenal ulceration. Gastric inhibitory peptide (Thomford, Sirinek, Crockett, Mazzaferrri & Cataland, 1974) and enteroglucagon (Bloom, Royston & Thomson, 1972) have been previously implicated in the pathophysiology of the dumping syndrome, and motilin, known to affect gastric motility (Christofides, Modlin, Fitzpatrick & Bloom, 1979), was also investigated in an attempt to define the possible role of these hormones in this enigmatic condition.

**Methods**

**Patients**

Thirty-nine patients were studied after surgery for duodenal ulcer, 20 of whom were completely symptom-free and the remaining 19, after similar surgical operations, experienced frequent symptoms of dumping (Meurling, 1953) in their daily lives. In addition, 20 patients were studied while awaiting surgery for their duodenal ulcer. The three groups were of similar mean age, weight and sex (Table 1). After an overnight fast, all patients received 75 g of glucose in 150 ml of water which they consumed within 3 min while lying in a semi-recumbent position. Any symptoms experienced during the test were carefully noted, including sweating, faintness, abdominal discomfort or distension and diarrhoea. Blood samples were taken from an indwelling cannula into heparin tubes containing aprotinin at 10, 20, 30, 40, 60, 90 and 120 min after glucose ingestion. Blood glucose (Hoffman, 1937), pulse rate and packed cell volume (Saunders, 1961) were monitored throughout.

**Hormone measurements**

Neurotensin was measured with a specific N-terminal reacting antiserum which detected two molecular forms in plasma (Blackburn & Bloom, 1979). Basal neurotensin-like immunoreactivity consisted almost entirely of a large molecular size form, which eluted from a Sephadex G-50 gel column in the void volume. This form is not affected by any known stimulus, whereas the rise in plasma neurotensin concentration after glucose consisted entirely of a form of small molecular size which eluted from a gel column in the identical position to the pure synthetic neurotensin. By using 125I-labelled synthetic neurotensin (Beckman Bioproducts, Geneva) of specific radioactivity 61 Bq/fmol, changes of 5 pmol/l of plasma were detected with 95% confidence.

Enteroglucagon was measured by first estimating total glucagon with an N-terminal reacting porcine glucagon antiserum (Thomson & Bloom, 1976), which also reacted maximally with human ileal glucagon-like immunoreactivity. Pure porcine ileal glucagon-like immunoreactivity (glicentin, gift of Dr A. J. Moody, Novo Research Institute, Denmark) was fully detected (97 ± 4%) by this assay. Pancreatic glucagon was measured specifically by a C-terminal reacting antiserum (Barnes & Bloom, 1976), which did not react with the intestinal material. The pancreatic glucagon concentration was subtracted from the total plasma glucagon-like immunoreactivity to yield the enteroglucagon concentration. The final assay sensitivity was 3 pmol/l of plasma.

Motilin was measured with an N-terminal reacting antiserum (Bloom, Mitznegg & Bryant, 1976), which detected both large and small molecular forms in plasma (Bloom, Christofides, Bryant, Buchan & Polak, 1979) and showed no cross-reactivity with other hormones. By using 125I-labelled porcine motilin, changes of 3 pmol/l of plasma could be detected with 95% confidence. Gastric inhibitory peptide was measured with a C-terminal reacting antiserum, which detected a large and small molecular form in plasma but showed no cross-reactivity with other hormones (Sarson, Bryant & Bloom, 1980). By using 125I-labelled porcine gastric inhibitory peptide (70 Bq/fmol), changes of 2.5 pmol/l of plasma were detected with 95% confidence.

Insulin was measured in plasma with commercially available reagents. Antiserum (Wellcome Research Laboratories, Beckenham, Kent, U.K.) at a final dilution of 1 in 8000 and 125I-labelled insulin (IM 38, The Radiochemical Centre, Amersham, Bucks., U.K.) with a specific radioactivity of 75 Bq/fmol enabled changes of 6 pmol/l of plasma to be detected with 95% confidence.

Statistical significance of results was determined with the Wilcoxon rank-sum test.

**Results**

The patient groups and operations performed are shown in Table 1. Patients who experienced postcibal symptoms in their daily lives also
developed one or more symptoms of dumping after oral glucose. The changes in pulse and packed cell volume in all patients are shown in Fig. 1. Considerable changes were observed in both parameters in the group of patients with dumping symptoms, in marked contrast to the much smaller alterations in the other two symptom-free groups.

Plasma levels of neurotensin, enteroglucagon and motilin after the glucose load are shown in Figs. 2 and 3, and Table 2 shows the peak incremental rise in all four hormones. Plasma neurotensin rose in all subjects after glucose (Fig. 3). In the pre-operative and postoperative symptom-free groups the rise was small, but an earlier and greater rise was seen in the patient group with dumping symptoms reaching a peak at 20 min (Table 2), as previously reported (Blackburn, Bloom, Ebeid & Ralphs, 1978). This last-named group of patients had a significantly greater rise in plasma neurotensin than the pre-operative and postoperative symptom-free groups for 40 min after glucose ingestion (P < 0.01 at 10 and 20 min, P < 0.05 at 30 and 40 min). Plasma enteroglucagon rose in all patients after oral glucose, reaching a peak at 40 min (Fig. 2). The group with dumping symptoms showed a greatly increased and sustained rise in plasma levels compared with the pre-operative subjects. The postoperative group without dumping symptoms had enteroglucagon levels intermediate between the two other groups. These levels were also significantly different from the symptomatic group throughout the test (P < 0.01 from 20 to 90 min, P < 0.05 at 120 min). The excessive rise in both plasma neurotensin and enteroglucagon in patients with dumping symptoms occurred independent of the type of operative procedure that had been performed. Mean plasma motilin levels rose in the dumping group after glucose ingestion (Fig. 2), reaching a maximum at 30 min, but the rise was not statistically significant compared with the other two patient groups. Indeed, there was considerable overlap between the patient groups, i.e. some symptomatic patients demonstrated a flat motilin response although others, who were symptom-free (both pre-operative and postoperative), had a substantial release of motilin into plasma.

Table 3 shows the changes in plasma insulin, gastric inhibitory peptide and blood glucose in the three patient groups. The rise in blood glucose observed during the test was greater and earlier in
Fig. 2. Plasma enteroglucagon (a) and motilin (b) in pmol/l in the three patient groups after ingesting 75 g of glucose. ▲, Pre-operative; ○, postoperative symptom-free; ●, postoperative with dumping symptoms.

Discussion

The dumping syndrome remains clinically important as a major complication of gastric operations for duodenal ulcer. A significant incidence of dumping has been noted even with the newer, more conservative procedure of highly selective or parietal cell vagotomy (Amdrup, Andersen & Høstrup, 1978). The pathophysiology of the dumping syndrome, induced by the ingestion of glucose as readily as after a mixed meal, has been extensively studied but the mechanisms involved are still incompletely understood. There is evidence that circulating factors play a significant role in this condition (Jesseph, 1968), but, to date, their nature has not been determined. We have investigated the plasma response of four hormones which might be considered candidates for this role: gastric inhibitory peptide and motilin derived from the upper intestine, and enteroglucagon and neurotensin from the distal small bowel.

An oral glucose tolerance test was used as a reproducible stimulus to provoke dumping. The faster rate of rise of blood glucose and hence plasma insulin concentrations seen postoperatively, especially in the patients with dumping symptoms, has been thought to be partly the result of a more rapid gastric emptying after vagotomy or partial gastrectomy (Cameron, Ellis, McGill & Le Quesne, 1969; Faxen, Berger, Kewenter & Kock, 1977). Changes in the enteroinsular axis have previously been reported in patients with the dumping syndrome (Thomford et al., 1974). Gastric inhibitory peptide is thought to have an important role in the enteroinsular axis (Andersen, Elahi, Brown, Tobin & Andres, 1978) and has previously been implicated in the dumping syndrome (Thomford et al., 1974). However, no significant difference in gastric inhibitory peptide release was found between the group of patients with dumping symptoms and the other two groups in this study.

Neurotensin is a newly discovered peptide hormone, found predominantly in specific endocrine cells in the ileal mucosa (Polak et al., 1978). The bovine tridecapeptide, originally isolated, has the same amino acid sequence as that found in man (Hammer, Carraway, Williams & Leeman, 1979). It has a wide range of potent pharmacological actions in experimental animals, though little is known of its physiological role in man. After the development of a highly sensitive plasma radioimmunoassay, a 10-fold greater rise has been found in patients who developed symptoms of dumping than in pre-operative controls. It is conceivable that neurotensin may therefore contribute to the observed fall in blood pressure and rise in packed cell volume seen in early dumping.

Motilin is produced by specific endocrine cells in the mucosa of the duodenum and jejunum (Polak, Heitz & Pearse, 1976). Infusion of motilin into healthy subjects, producing a rise in plasma motilin of approx. 60 pmol/l, caused gastric emptying of a mixed meal to increase by 50% (Christofides et al., 1979). It is possible that the greater rise of motilin seen in some of the symptomatic patients may have a pathophysio-
Neurotensin and the dumping syndrome

Fig. 3. Incremental rise in plasma neurotensin, in pmol/l, in the patient groups studied after ingesting 75 g of glucose. Values are expressed as increments above the mean of two basal values. Fasting levels of plasma neurotensin were similar in all groups (24 ± 2.6 pmol/l in pre-operative, 25 ± 2.1 pmol/l in symptom-free postoperative and 26 ± 2.8 pmol/l in the postoperative group with dumping symptoms). Increments are shown because the majority (> 95%) of basal plasma neurotensin is a very large molecular size, which appears to be unaffected by any known physiological stimulus. For symbols, see Fig. 2.

Table 2. Patient groups studied and corresponding incremental rises (above mean of two basal values) of the four peptide hormones at the times of the maximal rises seen in the symptomatic group

For neurotensin and gastric inhibitory peptide this occurred at 20 min, for motilin at 30 min and for enteroglucagon at 40 min after glucose ingestion. Values are expressed as means ± SEM: *P < 0.01 compared with the other two patient groups.

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<tr>
<th>Patient group</th>
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<th>Peak incremental rise (pmol/l)</th>
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<tr>
<td></td>
<td></td>
<td>Gastric inhibitory peptide</td>
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<tr>
<td>Pre-operative</td>
<td>20</td>
<td>14 ± 3.3</td>
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<tr>
<td>Postoperative asymptomatic</td>
<td>20</td>
<td>17 ± 3.2</td>
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<tr>
<td>Postoperative symptomatic</td>
<td>19</td>
<td>19 ± 3.5</td>
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logical role. However, dumping can also occur in the presence of a normal motilin response to oral glucose.

Enteroglucagon, a hormone produced mainly in the ileum (Bryant & Bloom, 1979) is thought to slow intestinal transit and influence mucosal growth (Bloom, 1972; Jacobs, Polak, Bloom & Dowling, 1976). The release of enteroglucagon, as previously reported, is markedly elevated in patients with dumping symptoms (Bloom et al., 1972). However, plasma levels exceeding those reported in this study have been found in subjects with other gastrointestinal diseases, for example, in coeliac disease (Besterman, Bloom, Sarson, Blackburn, Johnston, Patel, Stewart, Modigliani, Guerin & Mallinson, 1978) where dumping symptoms are absent. It is therefore unlikely that enteroglucagon has a direct role in the aetiology of dumping.

The complex pathogenesis of the dumping
A. M. Blackburn et al.

The dumping syndrome has been investigated for many years. It is possible that circulating hormones from the gastrointestinal tract may be involved in the pathophysiology of this condition. Plasma levels of neurotensin, a vasoactive peptide, were significantly elevated in patients with dumping symptoms. However, further work is required to establish whether it has a direct causative role or is merely another interesting but secondary phenomenon.

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References


Neurotensin and the dumping syndrome


