Serum Motilin in Gastrointestinal Diseases

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Abstract

In order to investigate the possible involvement of gastrointestinal hormones in functional disorders of the digestive tract, serum motilin, neurotensin and gastrin levels and their response to oral intake of fat and glucose were examined in patients with irritable colon syndrome and dumping syndrome. The following results were obtained. (1) Basal serum motilin levels were higher in patients with irritable colon syndrome than in normal subjects, and remained high after ingestion of either 50 g of butter or 50 g of glucose. (2) No consistent response in serum neurotensin levels was found in patients with irritable colon syndrome or in normal subjects. (3) An immediate increase in serum gastrin levels was found in response to fat ingestion both in patients with irritable colon syndrome and in normal subjects, but there was no difference between these two groups. (4) In a patient with typical dumping syndrome, a markedly high level of fasting serum motilin was found, and the level increased further after the oral intake of glucose. These findings suggest that motilin may be involved in the irritable colon syndrome and dumping syndrome.

Functional disorders of the gastrointestinal tract are characterized by various symptoms derived from the functional disturbance of the tract, but without any organic change. It can, therefore, be said that they are practically described in terms of what they are not; i.e., they are not anatomic or structural lesions and they are not identifiable metabolic entities, as mentioned in a textbook (Haubrich, 1976). This rather philosophical definition would be corrected, if any abnormality could be found in the behavior of gastrointestinal hormones in patients with these disorders. The recent advance in gut hormone research, particularly in the radioimmunoassay of these hormones, enabled us to look into this possibility.

Motilin is a 22 amino acid peptide (Brown et al., 1971 and 1973) which is present in the jejunal mucosa and circulates in a high concentration in human blood (Bloom and Polak, 1978). This hormone is implicated in the gastric motor activity (Brown, 1967) and in the interdigestive contractile activity of the entire gastrointestinal tract (Itoh et al., 1978). Therefore, it is of interest to investigate the possible involvement of this hormone in the irritable colon syndrome which is one of the functional disorders of the colon offering a number of clinical problems by a variety of symptoms such as abdominal pain, diarrhea or constipation. Another interesting functional disorder is the dumping syndrome, which is a complication after gastrectomy characterized by postprandial sweating, nausea and vertigo.

In this paper, we present the results of an attempt to approach the pathogenesis of
the irritable colon syndrome and dumping syndrome by determining the circulating concentration of motilin, neurotensin and gastrin after oral intake of fat and glucose, which are believed to cause the manifestation of the symptoms.

Materials and Methods

Eleven normal subjects and 27 patients with various gastrointestinal disorders, as listed in Fig. 2, were used. The normal subjects were all healthy volunteers ranging in age from 24 to 36 years. Nine patients with irritable colon syndrome were selected based on the presence of abdominal pain and diarrhea without any organic change detectable by X-ray examination, although the degree of their symptoms varied from occasional pain to frequent diarrhea with pain when the patients were examined. Four patients suffered from other colonic disorders; ulcerative colitis, megacolon, colon elongatum with severe constipation and enterocolitis of unknown etiology with more than 10 diarrhea attacks per day. One patient with idiopathic intestinal ulcer and 3 patients who received ileocolostomy were included in the study. In 5 patients with dumping syndrome, the symptoms varied from a simple nausea after meals to severe postprandial shock with nausea, sweating and a notable fall in blood pressure. As the control for dumping syndrome, 5 asymptomatic patients with partial gastrectomy by Billroth I were examined.

After an overnight fast, the patients were given orally 50 g of butter with a slice of bread or 50 g of glucose in solution. Blood samples were taken before and after the oral intake of butter or glucose and the sera were analysed for the concentration of motilin, neurotensin and gastrin. The concentrations of motilin and neurotensin were determined by Drs. N. and C. Yanaihara, Shizuoka Pharmaceutical College, or by Otsuka Assay Laboratory, and those of gastrin were determined in our laboratory using a modification of Yalow and Berson's method (Yalow and Berson, 1970).

Results

Fluctuation of basal levels of serum motilin in normal subjects

Since the serum motilin level fluctuates along with the interdigestive contraction of the gastrointestinal tract (Itoh et al., 1978), it was considered necessary to confirm that the basal levels showed a reasonably constant value for each case to test its response to the oral load of fat or glucose. Using 7 normal subjects, serum motilin levels were measured every 30 minutes starting at 9 a.m. under the fasting conditions, as shown in Fig. 1. None of the 4 patients tested 3 times from 9 to 10 a.m. showed a large variation, but a marked elevation of serum motilin levels was found in 2 cases tested for 3 hours; one with a peak at 10.30 a.m. and the other at 10.00 a.m. In one case, the level stayed reasonably constant during the 3 hour period.

Fasting serum motilin levels in patients with irritable colon syndrome in comparison with other intestinal disorders and in dumping syndrome

Fasting serum motilin levels were measured by taking the average of 3 determinations at around 9 a.m. (Fig. 2). In 9 patients with irritable colon syndrome, the serum motilin levels were in a range higher than that in 11 normal subjects, although
Fig. 2. Fasting serum motilin levels in patients with irritable colon syndrome, dumping syndrome and other gastrointestinal disorders compared with those in normal subjects.

A statistical comparison was not performed. A patient at the acute stage of ulcerative colitis with bloody stool and diarrhea showed a markedly higher serum motilin level whereas in 3 patients with other colonic disorders, e.g., megacolon, colon elongatum and enterocolitis, the levels were similar to the patients with irritable colon syndrome. The patients with ileocolostomy showed considerably higher levels than those found in normal subjects, but these findings can not be considered definitive with only 3 cases. The patient with severe dumping syndrome with nausea, sweating, vertigo and a fall in blood pressure after every meal showed a markedly high serum motilin level, but the other patients with dumping syndrome and the asymptomatic patients with gastrectomy had the levels similar to those in normal subjects.

Fig. 3. Fasting serum neurotensin levels in patients with irritable colon syndrome, dumping syndrome and other gastrointestinal disorders compared with those in normal subjects.

Fasting serum neurotensin levels in patients with irritable colon syndrome in comparison with other intestinal disorders and in dumping syndrome

Fasting levels of serum neurotensin were measured in patients with irritable colon syndrome, dumping syndrome and other intestinal disorders (Fig. 3.). In patients with intestinal disorders, no difference was found in the levels from those in normal subjects except for a markedly high level in the case with irritable colon syndrome. The level in the patient with typical dumping syndrome was not different from that in normal subjects.
Serum motilin response to oral fat in patients with irritable colon syndrome
The response of serum motilin levels to the oral intake of 50g of butter was studied in patients with irritable colon syndrome in comparison with that in normal subjects (Fig. 4). The levels remained higher in average in patients with irritable colon syndrome than in normal subjects, and a slight but immediate increase in the levels after ingestion of fat was also noticed in each case in both groups. However, large variations between patients made a statistical comparison impossible.

Serum motilin response to oral glucose in patients with irritable colon syndrome
The oral intake of glucose did not cause a consistent change in serum motilin levels (Fig. 5). The average levels of serum motilin before and after oral glucose were slightly higher in patients with irritable colon syndrome than those in normal subjects.

Serum neurotensin response to oral fat in patients with irritable colon syndrome
Changes in serum neurotensin levels after the oral intake of 50g of butter were studied in patients with irritable colon syndrome in comparison with those in normal subjects (Fig. 6). Because of the large variations between patients, it was impossible to make a meaningful comparison although the average levels were higher in patients with irritable colon syndrome than in normal subjects.

Serum gastrin response to oral fat in patients with irritable colon syndrome
The response of serum gastrin levels to oral intake of 50g of butter in patients with irritable colon syndrome is shown in Fig. 7 in comparison with that in normal subjects. A variety of patterns, from no response to a large immediate rise, was found in both groups although on the average the serum gastrin levels were increased by the oral intake of fat. There was no difference in the serum gastrin response between the patients and normal subjects.

Serum motilin response to oral glucose in patients with dumping syndrome
The response of serum motilin levels to the oral intake of 50g of glucose was studied in 4 patients with dumping syndrome.
in comparison with that in normal subjects (Fig. 8). No consistent response was found either in the patients or in normal subjects, and the levels stayed essentially unchanged by glucose intake. However, in one patient with typical symptoms (case 1), high levels with an additional increase at 60 to 90 minutes after the ingestion of glucose were noticed.

**Discussion**

The results obtained in this study were not definitive because of unexpectedly large variations between patients so that no statistical comparison could be performed. This is probably due to the following two reasons. (1) Clinical features of patients selected within a limited time were so varied that no distinct difference could be found even if an abnormality in the behavior of gastrointestinal hormones did exist. (2) The methods used to stimulate the release of the hormones into circulation were not adequate to see a strong and specific response of the circulating hormones. For instance, the direct application of fat or glucose into the duodenum by intubation should be considered for the next stage.

In spite of a large fluctuation in the fasting serum motilin levels, which confirmed the involvement of this hormone in the interdigestive contraction (Itoh et al.,...
1978), 3 determinations at 30 minutes intervals at around 9 a.m. confirmed that the basal level around this time of the day was reasonably constant. Therefore, the higher levels of fasting serum motilin levels in patients with irritable colon syndrome than in normal subjects seems to indicate that this hormone is involved in the manifestation of abdominal pain and diarrhea caused by spasms of the colon in this syndrome. An increase in serum motilin levels immediately after oral fat and after glucose ingestion was seen in patient with irritable colon syndrome. However, the fact that the serum gastrin levels were also increased by fat ingestion indicates that the gastric influences were included in the response of the duodenal hormones, and suggests the necessity of using more specific and direct stimuli to the duodenal mucosa than the ingestion of butter with a slice of bread in order to examine the behavior of these hormones in irritable colon syndrome.

The fasting serum motilin level was high in a patient with typical dumping syndrome, and the level remained high with an additional increase after the ingestion of 50 g of glucose. The serum motilin levels in dumping syndrome have not been studied before although a large increase in serum neurotensin levels in response to oral glucose in dumping syndrome was reported (Bloom et al., 1978). Although only one case with typical dumping syndrome was tested, the above finding points to the possible involvement of motilin in the manifestation of the syndrome.

The above findings suggest the possible involvement of motilin in the manifestation of irritable colon syndrome and dumping syndrome although the results are incomplete and not definitive. Further studies on this line of approach are in progress.

References