

Serum gastrin in duodenal ulcer

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Part II Effect of insulin hypoglycaemia

SUMMARY Serum gastrin has been measured by radioimmunoassay in normal subjects and patients with proven duodenal ulcer in response to insulin hypoglycaemia in conjunction with manoeuvres to decrease the intragastric acidity. Insulin hypoglycaemia alone caused a rise in the serum gastrin level from 5 ± 1.0 to 49 ± 2.9 pg/ml in duodenal ulcer and from 17 ± 5.6 to 42 ± 7.7 pg/ml in normals. With complete intragastric neutralization of acid and the same stimulus, the rise in duodenal ulcer was from 5 ± 1.3 to 128 ± 13.6 pg/ml and in normals from 13 ± 2.6 to 84 ± 2.6 pg/ml.

These studies suggest an increased production rate of gastrin in response to vagal stimulation in duodenal ulcer, and indicate the precise role of acid inhibition in the control of gastrin release and support the concept of both an increased 'G cell' mass and parietal cell mass in duodenal ulcer. They have also offered an explanation of the variable vagal stimulation of gastrin release in normal subjects.

As measured by an immunoassay based on antibodies to synthetic human gastrin I, basal serum gastrin levels in duodenal ulcer are low. Following stimulation with a protein meal, serum gastrin levels are raised to a significantly higher degree than in normal subjects (Korman, Soveny, and Hansky, 1971a). It is considered that low basal levels in duodenal ulcer are a result of inhibition of gastrin release by the large amount of acid in the stomach and that the increased protein-stimulated levels reflect an overproduction of gastrin in this disease.

In normal subjects serum gastrin response to vagal stimulation is variable, some showing a significant increase in levels, others showing no response (Korman, Soveny, and Hansky, 1971b). It has been suggested that this variability may in part be due to the effect of a concomitant release of acid which then suppresses the release of gastrin.

To assess the effect of vagal stimulation on gastrin release in duodenal ulcer and to gauge the influence of concomitant acid secretion on vagally stimulated gastrin, a series of studies was performed. In both normal control subjects and patients with duodenal ulcer, these studies were: (1) measurement of serum gastrin in response to insulin hypoglycaemia with

and without intragastric neutralization with sodium bicarbonate; (2) measurement of serum gastrin in response to intragastric bicarbonate alone.

Material and Methods

Four patients with radiologically proven duodenal ulcer and four normal subjects were each investigated on three separate occasions. Advised consent was obtained from all subjects. In each study the fasting subjects were intubated with a radioopaque nasogastric tube which was positioned fluoroscopically to ensure that the tip was placed in the antrum. The following experiments were then performed.

INSULIN HYPOGLYCAEMIA ALONE

Blood was collected for gastrin and glucose estimation at -30, 0, 10, 20, 30, 40, 50, 60, 75, and 90 minutes after intravenous insulin 0.2 units per kg body weight.

BICARBONATE ALONE

Blood was collected for gastrin estimation at -30, 0, 10, 20, 30, 40, 50, 60, 75, and 90 minutes during intragastric instillation of sodium bicarbonate solution (500 m-equiv/litre). At zero time the

stomach was aspirated and 50 ml (25 m-equiv) of sodium bicarbonate instilled rapidly via the nasogastric tube, followed by the constant infusion of bicarbonate solution at a rate of 100 ml (50 m-equiv) per hour for 90 minutes.

INSULIN HYPOGLYCAEMIA WITH BICARBONATE

The above study was repeated in an identical manner except that at zero time in addition to beginning the intragastric instillation of bicarbonate an intravenous injection of insulin 0.2 units per kilogram body weight was given. Blood was collected at the same times for gastrin and glucose estimation.

Blood glucose was estimated using the glucose oxidase method on an autoanalyzer. The serum gastrin was estimated in duplicate by immunoassay as previously described (Hansky and Cain, 1969; Hansky, Soveny, and Korman, 1971).

Statistical analysis was by use of the Student's *t* test on unpaired samples (Snedecor and Cochran, 1968).

Results

Figures 1 and 2 show the blood glucose and serum gastrin responses to insulin hypoglycaemia alone, bicarbonate alone, and insulin hypoglycaemia with concomitant intragastric bicarbonate instillation in four patients with duodenal ulcer and four normal subjects respectively.

INSULIN HYPOGLYCAEMIA ALONE

In patients with duodenal ulcer the serum gastrin level rose significantly from a basal level of 5 ± 1.0 pg/ml to a peak of 49 ± 2.9 pg/ml at 10 minutes after the greatest fall in blood glucose ($P < 0.0005$).

In normals there was a smaller but significant rise in serum gastrin from 17 ± 5.6 pg/ml to 42 ± 7.7 pg/ml at 10 minutes after the greatest fall in blood glucose ($P < 0.05$). The increase in serum gastrin in duodenal ulcer was significantly greater than the increase in normals ($P < 0.05$).

BICARBONATE ALONE

In patients with duodenal ulcer the serum gastrin rose significantly from a basal level of 6 ± 1.9 pg/ml to 40 ± 11.7 pg/ml at 40 minutes after commencement of instillation and it remained steady at about this level while decarbonate instillation was continued. At the completion of the study it was 43 ± 8.8 pg/ml ($P < 0.025$).

In normals there was also a significant rise in serum gastrin from 13 ± 1.9 pg/ml to 36 ± 4.1 pg/ml at 30 minutes after the start of the instillation and it remained steady at about this level while bicarbonate instillation continued. At the com-

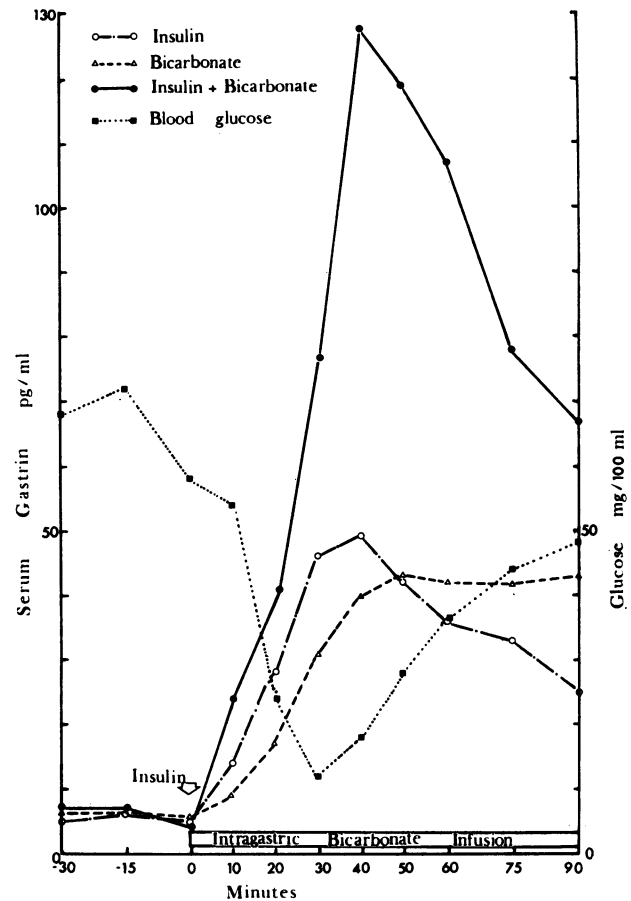


Fig. 1 Serum gastrin response to insulin hypoglycaemia, neutralization with sodium bicarbonate, and a combination of insulin hypoglycaemia and bicarbonate neutralization in four patients with duodenal ulcer. Blood glucose response to insulin is also shown.

pletion of the study it was 33 ± 4.1 pg/ml ($P < 0.0025$). The rise above basal levels with acid neutralization was not significantly different in the two groups.

INSULIN HYPOGLYCAEMIA WITH BICARBONATE

In patients with duodenal ulcer there was a significant rise in serum gastrin from a basal level of 5 ± 1.3 pg/ml to a peak of 128 ± 13.6 pg/ml at 10 minutes after the greatest fall in blood glucose ($P < 0.0005$). The serum gastrin level was still significantly raised at the completion of the study (67 ± 12.0 pg/ml, $P < 0.0025$).

In normals there was also a significant but smaller rise in serum gastrin from 13 ± 2.6 pg/ml to 84 ± 2.6 pg/ml at 10 minutes after the greatest fall in blood

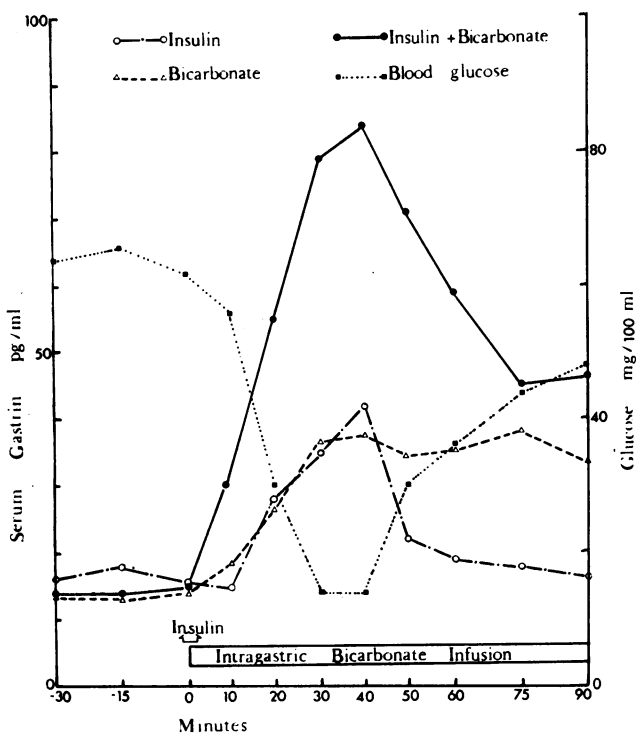


Fig. 2 Serum gastrin response to insulin hypoglycaemia, neutralization with sodium bicarbonate, and a combination of insulin hypoglycaemia and bicarbonate neutralization in four normal subjects. Blood glucose response to insulin is also shown.

glucose ($P < 0.0005$). The serum gastrin level was still significantly raised at the completion of the study (46 ± 6.7 pg/ml, $P < 0.005$). The rise in serum gastrin in duodenal ulcer was again significantly greater than the corresponding rise in normal subjects ($P < 0.0025$).

Discussion

These results indicate that vagal stimulation by insulin hypoglycaemia in patients with duodenal ulcer consistently produces a significantly greater rise in serum gastrin than it does in normal control subjects. This corroborates the evidence suggested by the protein meal studies of an increased amount of released gastrin from the antrum in duodenal ulcer and this may be due to an increase in numbers of G cells in the antrum which respond to both local and vagal stimulation.

The precise dependence of gastrin release on the acidity of the juice bathing the antrum is illustrated by the significantly greater response achieved with removal of acid inhibition. In patients with duodenal

ulcer, vagal stimulation without interference to the acid inhibitory mechanism raises the serum gastrin by 44 pg/ml, whilst with complete intragastric neutralization of acid the rise above basal levels is 123 pg/ml. By contrast, the corresponding figures in normal subjects are a rise of 25 pg/ml with vagal stimulation and intact acid inhibitory mechanism, and a rise of 71 pg/ml after complete acid neutralization.

What conclusions can be drawn from these results? The role of the vagus in the stimulation of acid secretion by the stomach is complex. Pevsner and Grossman (1955) have shown that vagal stimulation can act on the parietal cell to produce acid after extirpation of all gastrin-containing tissue in the dog. In addition to this direct action on parietal cells, it is now known that vagal stimulation causes release of gastrin (Fyrö, 1967; Korman *et al*, 1971b). That there is an interplay between the two mechanisms has been shown by the diminished response of parietal cells to gastrin and histamine after vagotomy (Andersson and Grossman, 1965).

It appears as if vagal stimulation in normals does not elicit a marked rise in serum gastrin, although serum gastrin does rise significantly above basal levels. Korman *et al* (1971b) reported that the serum gastrin response to vagal stimulation in this group is variable, some showing a significant increase in levels, others showing no response. They postulated that in the latter acid was concomitantly released thus inhibiting gastrin release, and indeed speculated that this group may be prone to develop duodenal ulcer. The present findings would suggest that the reverse may be true. Normal subjects who show a significant rise in serum gastrin with vagal stimulation may be similar to duodenal ulcer patients with increased acidity and low basal gastrin levels. Stimulation in these subjects results in a greater gastrin release due either to increased gastrin content of G cells, increased numbers of G cells consequent upon increased vagal drive, or increased sensitivity of G cells to vagal stimulation. On the other hand, those normals with a poor response are unlikely to develop duodenal ulcer, and in this group, relatively higher basal gastrin levels are found in association with less basal acid secretion. Following vagal stimulation in these latter subjects, acid secretion increases, antral pH falls, inhibition is now maximal, and gastrin release is relatively small as the G cells are 'normal' both in regard to population and to function.

In patients with duodenal ulcer there is a balance between release and inhibition of gastrin but inhibition is maximal in the basal state and hence gastrin levels are low. When vagal stimulation is applied, inhibition remains the same but because of an increased number of G cells, the stimulus elicits

a greater rise in serum gastrin. When inhibition is diminished by acid neutralization, gastrin is released in even greater amounts.

Dragstedt (1969) has proposed that the basic defect in duodenal ulcer is an increased vagal drive which causes hyperplasia of parietal cells. The present results indicate that the increased vagal drive, or other undetermined stimulus, not only causes hyperplasia of parietal cells but also an increase in number of G cells in duodenal ulcer. However, the drive is probably greater on the parietal cells, and the high acidity therefore effectively inhibits the release of gastrin in the basal state. Thus, by inference, gastrin plays little part in the genesis of the increased parietal cell mass in duodenal ulcer. However, the relatively high levels of gastrin achieved after food or vagal stimulation may contribute to this increased parietal cell mass.

It is stressed that another group (Byrnes, Young, Chisholm, and Lazarus, 1970), using an immunoassay based on antibodies to the C-terminal tetrapeptide of gastrin, find high basal levels in duodenal ulcer and suggest that the vagus acts predominantly on the antrum—rather than on the parietal cell. They may well be measuring a different component of gastrin, or another similar peptide, which does not readily suppress with acid and which does not cross react with our particular antiserum to synthetic human gastrin I. These important differences may well hold the key to the pathogenesis of duodenal ulcer.

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