Gastrin response to meals of different composition in normal subjects

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SUMMARY  The serum gastrin responses and the integrated gastrin responses to eating three meals of very different composition were studied in the same normal subjects on different days. Two meals, a milk meal of 500 ml, and a breakfast of eggs, toast, butter, marmalade, fruit juice and coffee, were eaten at breakfast time. The serum gastrin responses to these meals were compared and contrasted with the concentrations observed when the subjects fasted over the same time of day. A steak meal was eaten at lunch time. There were no significant differences between the mean serum gastrin concentrations to the three meals but each meal produced a significant increase in serum gastrin above fasting levels. When the prefeeding gastrin concentration was subtracted from the gastrin responses then the integrated responses to the steak meal were greater than those to either of the breakfast meals.

Considerable variability in response to any one meal was observed within the group of subjects, but those subjects who produced high serum gastrin concentrations to one meal did so to the others. Conversely, a low response to one meal was reflected in low responses to the other two meals. Fasting serum gastrin concentration was correlated with the age of the subject. Repeatability of the response to one meal was tested in two subjects who ate the same meal on four separate occasions showing their responses to be repeatable.

In the past decade the radioimmunoassay of gastrin has provided a new and sensitive tool which enables gastroenterologists to measure plasma gastrin concentrations in all manner of conditions, including the Zollinger-Ellison syndrome (Isenberg, Walsh, Passaro, Moore, and Grossman, 1972). The hypotheses involving vagal release of gastrin (Maung Pe Thein and Schofield, 1959) have been amply confirmed as has the inhibition of gastrin release by acidification of the antrum (Ganguli and Hunter, 1972).

In the quest to understand better the physiology of gastric secretion and to investigate the possible role of gastrin in the aetiology of peptic ulceration, different workers have used a variety of meals to stimulate and study gastrin secretion. The composition of the meals have ranged from two Oxo cubes (Byrnes, Young, Chisholm, and Lazarus, 1970), through a standard breakfast of boiled eggs, fruit juice, toast, marmalade and coffee to the more substantial steak meal and a sweet (Wyllie, Boulos, Lewin, Stagg, and Clark, 1972).

The protein, fat, carbohydrate and caloric value of these meals varies greatly and yet there is no apparent relationship between these constituents and the resulting plasma gastrin. For example, the responses reported by Byrnes et al (1970) to two Oxo cubes was 4700 pg/ml whereas that to eggs, steak, cheese and milk (Reeder, Jackson, Ban, Davidson, and Thompson, 1970) was a mean 78 pg/ml. Any comparison of these values is virtually prohibited by the existence of two major variables between different laboratories. First, different antisera were used in each laboratory and the characteristics of these are almost certainly different such that the ‘gastrin’ concentration of the same sample would differ, dependent upon the antisera used (Hansky, Soveny, and Korman, 1974).

Secondly, no comparison has been made of the responses of the same subjects to different meals in the same laboratory. There are considerable variations in fasting gastrin in samples from normal subjects in each laboratory (table IV for details) suggesting that there is a considerable spread of fasting
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Gastrin in the normal population which may well be reflected in the stimulated responses, illustrating the danger of making comparisons between different small groups. Furthermore, no analysis has been made of the repeatability of the gastrin response to any one meal in the same subject and, therefore, there remains the possibility that the great variability in responses to different meals reflects the variability of each subject.

Without a strict characterization of these responses to various meals, coupled with strictly characterized assay systems, it is impossible to compare the values from different laboratories and therefore to obtain baseline normal data with which comparisons of suspect pathophysiological conditions can be made.

We have compared the plasma gastrin responses of a group of subjects to three meals of widely different composition. In two subjects the responses were studied to one meal repeated on a number of occasions.

**Methods**

Eleven male volunteer subjects free of dyspepsia (mean age 33.3 ± 2.5 years) were studied on a number of occasions. Following an overnight fast an indwelling intravenous cannula was inserted into a forearm vein the next morning and two fasting samples were collected at 15-minute intervals. Subjects ate either the standard breakfast of two boiled eggs, coffee, two slices of toast, butter and marmalade and 150 ml of orange juice, or drank the milk meal of 200 ml of milk concentrate (Carnation Foods Ltd) diluted to 500 ml with water, or they continued to fast.

The third meal was eaten three and a half hours after a standard breakfast by subjects who had fasted overnight. This meal was a steak lunch of 200 g lentil soup, 200 g steak, 100 g creamed potatoes, 50 g peas and gravy, followed by dessert of caramel creme or fruit salad and coffee. Plasma samples were collected 15 min before and immediately before eating. Following the completion of each meal or during the prolonged fast blood samples were taken at 15, 30, 45, 60, 75, 105, 135, 165 and 195 minutes. Samples were collected into plain tubes, allowed to clot, and serum samples stored at −20°C for subsequent assay of gastrin.

Serum gastrin concentration was determined by radioimmunoassay using purified, mono-iodinated SHGI as the label (Stadil and Rehfeld, 1972) and an antibody raised in rabbits against the hexadecapeptide 2-17 sequence covalently by carbodiimide to bovine serum albumin (McGuigan, 1968).

The binding energy expressed by the equilibrium constant was 4 × 10⁻¹¹ litres/mol and the sensitivity of the assay (detection limit) was 0-9 pg/tube giving a normal working range of 10 to 1000 pg/ml of serum. The antisera crossreacts equally on a molar basis with pure human big gastrinI in the ratio of 1:86 with pentagastrin (ICI 50123) and 1:54 with the approximately 15% pure CCK/PZ. Within-assay precision was calculated as the 95% confidence limits of at least 48 replicates of each dose of the standard curve of 2.5, 10, 20 and 50 pg and was 0-7, 0-7, 1-2 and 1-7 pg respectively. The between-assay reproducibility was assessed as the coefficient of variation of three serum samples assayed on a number of occasions over three months and these were between 10 and 15%.

The serum gastrin values are calculated as pg = SHGI/ml and as the integrated serum gastrin responses, these being calculated as the area under the curve described by serum gastrin concentrations and the time studied. Both serum gastrin concentrations and integrated responses have also been calculated as the response above fasting value observed before the meal. The gastrin concentration after the meal is calculated by subtracting the fasting gastrin concentration immediately before the meal and the integrated gastrin responses after the meal by subtracting the integrated fasting gastrin calculated from the fasting concentration before the meal and the duration of the feeding response.

The results have been expressed as mean ± 1 SEM (N) and analysed for significance of difference between means using Student's t test or Cochran's modification of this test. In appropriate cases the Wilcoxon rank test for paired data has been used. Regression analysis is by the method of least squares and calculation of slope (m), regression coefficient (r) and intercept (c).

<table>
<thead>
<tr>
<th>Breakfast Carnation Milk Fasting Steak</th>
</tr>
</thead>
<tbody>
<tr>
<td>First mean fasting ± 1 SEM 33·9 ± 13 29·1 ± 10·8 28·3 ± 8·6 20·0 ± 7·8</td>
</tr>
<tr>
<td>Second mean fasting ± 1 SEM 24·1 ± 10 28·9 ± 10·4 28·7 ± 10·0 14·4 ± 6·2</td>
</tr>
<tr>
<td>Paired n 10 10 11 10</td>
</tr>
</tbody>
</table>

Table 1 Fasting plasma gastrin concentration taken before each meal or fasting

1 All values are expressed as pg = SHG l/ml serum. There was no significant difference between any pair of observations (p > 0·4 in each case).
Fig 1  The relationship between fasting serum gastrin concentration and the age of the subjects. Points represent means and the bars 1 SEM.

Results

FASTING VALUES
The fasting serum gastrin concentrations for the whole group (table I) show no significant differences between either the first or second estimations before each meal or between any of the mean values. The values obtained after an overnight fast show a direct relationship with the age of the subject (fig 1). During the prolonged fast there was no significant change in the mean serum gastrin concentration (fig 2).

SERUM GASTRIN CONCENTRATIONS IN RESPONSE TO STANDARD MEALS

Breakfast
The mean concentration of serum gastrin rose from a fasting 24·1 ± 10 pg/ml to a peak of 69·4 ± 11·4 pg/ml (11) 45 minutes after finishing the meal and remained significantly elevated for two and a quarter hours (fig 2).

The milk meal
The mean serum gastrin concentration rose from a fasting mean of 28·9 ± 10·4 pg/ml to a peak 65·8 ± 13·4 pg/ml (10) one hour after completing the meal and remained significantly elevated for two and a quarter hours (fig 3).
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The mean serum gastrin rose to a peak value of 84.2 ± 32 pg/ml (10) 105 min after finishing the steak meal but this cannot be analysed for significance above fasting since no fasting study was made at this time of day (fig 4).

A comparison of the responses at equal intervals after finishing eating showed no significant differences between the means in response to any meal. There was no significant difference between the mean times taken for the same eight individuals to reach peak response to breakfast (0.59 ± 0.18 hr or milk 0.88 ± 0.8 hr, P > 0.2) but these times were significantly less than the mean time taken to reach peak following steak (1.59 ± 0.32 hr, P < 0.01 in each case).

INTEGRATED GASTRIN RESPONSES IN RESPONSE TO STANDARD MEALS

The total integrated gastrin responses to the three meals showed no significant differences between the means (P > 0.05 in each case, table II). The responses calculated by subtracting the fasting values from the total revealed significant differences between the responses to the milk meal and the steak.
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Peak serum gastrin concentrations following breakfast and after carnation
pg/ml

Peak after steak v Peak after breakfast
○ m = 1.8596
corr. coef. = 0.9661
p = < 0.01

Peak after carnation v Peak after breakfast
● m = 0.9666
corr. coef. = 0.7638
p = < 0.025

Fig 5 Relationship between the peak serum gastrin concentrations following breakfast and the steak meal (○) and between the breakfast and the milk meal (●) in normal subjects.

meal and between breakfast and the steak meal in eight subjects who ate each meal (table II).

There are considerable variations in the mean peak responses to each meal but any one subject responds similarly; eg, a subject who produces a large peak response to one meal produces a large response to the other meals (fig 5). This relationship is equally clear for log integrated gastrin responses to breakfast and log integrated gastrin responses to either milk (r = 0.8393, p < 0.01, df6) or steak (r = 0.7909, p < 0.02, df6).

Neither the peak nor the integrated gastrin responses to any meal were correlated with the age of the subject (p > 0.2 in each case).

The reproducibility of the serum gastrin concentration following the breakfast meal was tested in two subjects, one of whom (ELB) showed a small response and the other (JDR) a large response when tested in the original series. Both subjects ate the standard meal on four occasions during a period of

either four (ELB) or nine months (JDR). Each subject's responses showed variability but this was not sufficient to obscure the serum gastrin pattern characteristic of each person (fig 6).

Discussion

The mean fasting serum gastrin concentrations determined on at least three occasions in each subject following overnight fasting (table I) are similar to the majority of the recently published values (table III). Where differences exist these may be attributable to the antibodies and labels used in the various laboratories but could be in part caused by the selection of subjects from a very heterogeneous population. The need to standardize the time of day and the preceding fasting conditions is illustrated by the observation that the serum gastrin concentrations observed in eight subjects three and a half hours after eating a standard breakfast, immediately before eating lunch (15.1 ± 4.8 pg/ml) are significantly lower than those observed after an overnight

Table III Dietary content of the three standard meals

<table>
<thead>
<tr>
<th>Meal</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Carbohydrate (g)</th>
<th>Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>18.0</td>
<td>31.0</td>
<td>65.0</td>
<td>610</td>
</tr>
<tr>
<td>Milk</td>
<td>17.0</td>
<td>18.3</td>
<td>26.7</td>
<td>366</td>
</tr>
<tr>
<td>Steak</td>
<td>75.6</td>
<td>65.6</td>
<td>86.4</td>
<td>1300</td>
</tr>
</tbody>
</table>
Gastrin response to meals of different composition in normal subjects

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mean Gastrin Concentration (pg/ml)</th>
<th>SEM</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansky, Sovery, and Korman (1973)</td>
<td>36</td>
<td>1.7</td>
<td>264</td>
</tr>
<tr>
<td>Muller, Fritsch, Rick, and Hausam (1973)</td>
<td>82</td>
<td>7.1</td>
<td>33</td>
</tr>
<tr>
<td>McGuigan and Trudeau (1971)</td>
<td>85</td>
<td>9.8</td>
<td>35</td>
</tr>
<tr>
<td>Stadil and Rehfeld (1973)</td>
<td>52</td>
<td>4.6</td>
<td>120</td>
</tr>
<tr>
<td>Gedde-Dahl (1974)</td>
<td>65:9</td>
<td>2.9</td>
<td>205</td>
</tr>
<tr>
<td>Berson, Walsh, and Yalow (1973)</td>
<td>30</td>
<td>5.0</td>
<td>71</td>
</tr>
<tr>
<td>Gangui and Hunter (1972)</td>
<td>105</td>
<td>7.0</td>
<td>113</td>
</tr>
<tr>
<td>Bunchman, Reeder, and Thompson (1971)</td>
<td>123</td>
<td>10.0</td>
<td>15</td>
</tr>
<tr>
<td>Maxwell, Moore, Dixon, and Steven (1971)</td>
<td>35</td>
<td>2.1</td>
<td>14</td>
</tr>
<tr>
<td>Schrumpf and Sand (1972)</td>
<td>62</td>
<td>7.0</td>
<td>21</td>
</tr>
</tbody>
</table>

Table IV  Examples of the published mean fasting gastrin concentrations in normal subjects

The peak responses to the three meals are shown in table II and compared with published values in table V. It is surprising, in spite of the considerable variation in composition and caloric values of the three meals (table III), that the responses are so similar. This similarity is evident in the reported responses to meals of even more varied composition (table V). We do not as yet know whether the acid secretory responses to meals of such varied composition differ in either magnitude or duration. If a more substantial meal does produce greater gastric acid secretion this cannot, from our evidence, be accounted for by differences in the gastrin concentration or the total integrated gastrin responses (table II).

It may be, however, that the different gastrin molecular species are released in different proportions in response to the various components of the meals. The major forms of gastrin reported to be released in response to feeding in man are the little and big gastrins. Little gastrin is biologically more active on a molar basis than both big gastrin and mini gastrin when tested in the dog (Debas, Walsh, and Grossman, 1974). Our antibody reacts equally

Table V  Comparison of the published mean peak serum gastrin concentrations in response to meals of various compositions
on a molar basis with big and little gastrin and is sensitive to mini gastrin (Blair, Grund, Lund, Reed, and Sanders, 1975). It is, therefore, possible that the similar total gastrin concentrations and total integrated responses to the three meals disguise different biological activities.

When the responses to the three meals are analysed by subtraction of the immediate preceding fasting value or the integrated fasting value, then the peak and the integrated responses to the steak meal are significantly greater than those to breakfast and to the milk meal, whereas the responses to milk and breakfast are not significantly different from one another (table II).

If the acid secretory response to the meat meal is greater than to the other meals, and this is due only to gastrin stimulation, then the parietal cell must be sensitive to changes in serum gastrin concentration rather than to the absolute concentration. It is, however, probable that a number of factors modify the response to gastrin, eg, vagal synergism may be greater during the meat meal. Should the acid response to the steak meal be no greater, then the demonstrated greater change in gastrin response (table II) must be meaningless and possibly artefactual.

The differences between responses-basal values to the three meals owe much to the fact that the fasting responses, subtracted from the peak and total integrated responses, are significantly lower before the steak meal than to the other two meals. Whether these differences are real or artefactual can only be resolved by carrying out fasting studies over the lunch period, preceded both by an overnight fast and by a meal at breakfast. The previously published evidence of plasma gastrin concentrations studied over the 24-hour period does not suggest that there are low concentrations immediately before lunch (Moore and Wolfe, 1973; Ganguli and Forrester, 1972) as compared with early morning.

There was a significant correlation between the gastrin responses to different meals in each subject (fig 5), confirming the fact that each subject responded consistently, ie, subjects who produced low responses to any one meal did so to the other meals and vice versa. The reproducibility of the gastrin response was tested in two subjects (fig 6). Although there was variation from test to test this was not such that it obscured the fact that one subject had a consistently low gastrin profile and the other a consistently high profile.

In conclusion it appears that the total gastrin concentrations and total integrated responses following each of the three meals are very similar. This similarity of response, in spite of the marked differences in the composition and size of the meals, may well indicate the existence of normal effective feedback mechanisms controlling the gastrin response.

Some pathophysiological conditions of the gastrointestinal tract may result from a failure of these feedback mechanisms to control the plasma gastrin concentrations. In such circumstances investigation of the gastrin responses to these three meals may prove to discriminate between these states and normals.

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