Relationship between insulin- and histamine-stimulated gastric secretion before and after vagotomy

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SUMMARY The relationship of gastric secretion in response to a single injection of insulin and in response to a histamine infusion, in unoperated patients with duodenal ulcer was studied before and after vagotomy. The secretion in response to insulin was significantly less than that in response to histamine. The ratio was about 0.7 before vagotomy, and about 0.4 after vagotomy irrespective of the adequacy of vagotomy. Highly significant correlations were obtained between the responses to the two stimuli, both in the unoperated group and in the whole postoperative group as well as in the inadequate vagotomy group, but not in patients after adequate vagotomy. Thus, the proportional differences between individuals in response to insulin were substantially the same as the proportional differences in response to histamine. The algebraic excess of histamine over insulin-stimulated secretion before vagotomy did not differ from the value after vagotomy. Histamine-stimulated secretion after adequate vagotomy approximated to, but after inadequate vagotomy was greater than the preoperative algebraic excess of histamine over insulin-stimulated secretion. These results are consistent with a new model of acetylcholine/histamine-receptor relationships. A certain proportion of the parietal cells are insensitive to the vagus but sensitive to histamine; and those sensitive to the vagus are also sensitive to histamine, but only when their vagal innervation is intact.

Previous work on the relationship between gastric acid secretion stimulated by insulin hypoglycaemia and that in response to histamine as a maximal stimulus has yielded conflicting results. Some workers have suggested that insulin-stimulated gastric secretion was the same as or greater than histamine-stimulated secretion, while others found the reverse. Possible sources for the discrepancy are failure to correct for duodenogastric reflux or failure to use histamine (or pentagastrin) in a manner producing truly maximal secretion.

In this study of the relationship of insulin- and histamine-stimulated secretion, histamine was therefore given by a method known to achieve maximal secretion—the continuous infusion technique of Lawrie et al—and errors caused by pyloric losses and by duodenogastric reflux were measured and corrected. The effect of vagotomy on this relationship has been examined by studying patients with duodenal ulcer before and after vagotomy.

Methods

PATIENTS

Studies were performed in unoperated patients with duodenal ulcer and in patients after vagotomy for duodenal ulcer. A careful clinical follow up of the latter group was carried out; all patients had had their operations at least two years previously (range two to 29 years, median 3.3 years).

Each patient had an insulin test (0.2 u/kg soluble insulin by single intravenous injection with collections for two hours) immediately followed by a histamine-infusion test (0.13 nmol histamine acid phosphate/kg/h, 0.04 mg/kg/h for one hour). The observed volume of each 10 minute sample was corrected for pyloric losses and duodenal reflux. The volume of secretion after these corrections was designated as \( V_G \) ml/10 min. The sum of the volumes collected during the period one-half to two
hours after the injection of insulin was divided by 1.5 to express the rate of secretion as $\frac{1}{2}V_G$ ml/hour. After histamine the maximal plateau secretion was determined and expressed as maximal $V_G$ in ml/hour. The raw data of uncorrected volumes and acid outputs were also examined.

Secretion data were obtained in 81 unoperated patients and in 81 patients (not identical but with considerable overlap) after vagotomy. The post-vagotomy results are given for the whole group and also for two selected subgroups: (a) 25 patients with recurrent ulcer diagnosed either on gastroduodenoscopy or at further operation and (b) 29 asymptomatic patients who were considered to have had an adequate vagotomy according to gastric secretory data described elsewhere.

The relationship between insulin- and histamine-stimulated secretion was studied by examining the (1) mean secretion rates, (2) correlation/regression analysis and (3) secretion ratios.

In order to explore further a hypothesis proposed in our discussion, the secretion values in 43 patients who had studies both before and after vagotomy were analysed. There were 11 patients with proven recurrent ulceration diagnosed by gastroduodenoscopy or at laparotomy and 22 asymptomatic patients whose postoperative secretion fulfilled the criteria for adequacy of vagotomy in terms of insulin $\frac{1}{2}V_G$. The differences between the volumes of secretion with histamine- and with insulin-stimulation were also examined in all groups.

All parametric statistical tests were performed after natural logarithmic transformation to a normal distribution. The arithmetical equivalent values of logarithmic group means and 95% tolerance limits are given; the standard deviations of these means cannot be expressed in arithmetical terms and so are not given. Comparison between paired data was made by the paired $t$ test and between group means by the unpaired $t$ test, both after logarithmic transformation. Comparison between the slopes of the regression lines was made by the $t$ test. When necessary non-parametric tests (Wilcoxon's rank sum test for paired observations) were used.

### Results

**Unoperated Patients**

Firstly, histamine-stimulated secretion was significantly greater than insulin-stimulated secretion (Table 1).

Secondly, there was a highly significant correlation between the logarithmic values of insulin- and histamine-stimulated secretion and the slope of the regression line did not significantly differ from unity (Fig. 1, Table 2). In other words, over the whole group of patients proportionate differences in histamine-stimulated secretion were matched *pari passu* by the proportionate differences in insulin-stimulated secretion.

Thirdly, the mean ratios of insulin- and histamine-stimulated secretion was 0.64 but there was a wide range (Table 3).

**Post Vagotomy Patients**

Firstly, the mean histamine-stimulated secretion was significantly greater than the mean insulin-stimulated secretion in the whole group and in each subgroup (Table 1).

Secondly, highly significant correlations between insulin- and histamine-stimulated secretion were present in the whole group and in the 25 patients with recurrent ulcer (Figs. 2 and 3). In the group with adequate vagotomy, however, there was no correlation (Fig. 4). In the subgroup with recurrent ulceration, the regression line did not differ significantly from unity, but for the whole group the slope was significantly less than unity (Table 2). Thus, after vagotomy the correlation between insulin and histamine responses is set at a lower value than unity.

Thirdly, the insulin/histamine ratios were 0.41 for the whole group, 0.46 for the patients with recurrent ulcer and 0.41 for patients with adequate vagotomy. The range, however, was very wide (Table 3).

### Table 1  Mean values of histamine- and insulin-stimulated secretion and comparison between paired data

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>No</th>
<th>Histamine Max $V_G$ ml/h</th>
<th>Insulin $\frac{1}{2}V_G$ ml/h</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unoperated patients</td>
<td>81</td>
<td>321.0</td>
<td>196.0</td>
<td>10.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All postvagotomy patients</td>
<td>81</td>
<td>152.0</td>
<td>58.0</td>
<td>13.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with recurrent ulcer</td>
<td>25</td>
<td>246.0</td>
<td>107.0</td>
<td>9.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with adequate vagotomy</td>
<td>29</td>
<td>88.0</td>
<td>31.0</td>
<td>8.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
of the unoperated group, the whole postvagotomy group and the recurrent ulcer group (Table 2).

Secondly, the insulin/histamine ratios before vagotomy were significantly greater than those after vagotomy for all postvagotomy patients and also for each subgroup separately (Table 3). The recurrent ulcer and the adequate vagotomy subgroups, however, did not differ in their mean ratios.

**COMPARISON BETWEEN DIFFERENCES IN HISTAMINE- AND INSULIN-STIMULATED SECRETION IN PATIENTS BEFORE AND AFTER VAGOTOMY**

The algebraic excess of histamine- over insulin-stimulated secretion before vagotomy did not differ from the value after vagotomy when compared by the Wilcoxon's rank sum test in the whole group and in the subgroups of patients with adequate and those with inadequate vagotomy (Table 4). Thus the responses to both secretagogues after vagotomy diminished in proportion to the extent of vagal section, but a constant difference in response to the two secretagogues was maintained. In patients with adequate vagotomy, the histamine-stimulated secretion approximated the preoperative excess of histamine- over insulin-stimulated secretion. In patients with recurrent ulceration, however, the postoperative histamine-stimulated secretion was

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**Table 2** Correlation coefficient (r) of natural logarithm of insulin-stimulated secretion against natural logarithm of histamine-stimulated secretion. Also listed are slopes of regression lines, tests for difference of those slopes from unity, and comparison between the slopes of regression line in unoperated patients with slopes of regression line in other groups.

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>No</th>
<th>Correlation coefficient</th>
<th>Slope of the regression line</th>
<th>Test of slope against unity</th>
<th>Test of post-vagotomy slopes against unoperated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unoperated patients</td>
<td>81</td>
<td>0.737 * &lt;0.001</td>
<td>1.003</td>
<td>0.006 NS</td>
<td>0.06 NS</td>
</tr>
<tr>
<td>All postvagotomy patients</td>
<td>81</td>
<td>0.617 * &lt;0.001</td>
<td>0.731</td>
<td>2.57 &lt;0.02</td>
<td>0.56 NS</td>
</tr>
<tr>
<td>Patients with recurrent ulcer</td>
<td>25</td>
<td>0.721 * &lt;0.001</td>
<td>1.024</td>
<td>0.117 NS</td>
<td>0.04 NS</td>
</tr>
<tr>
<td>Patients with adequate vagotomy</td>
<td>29</td>
<td>0.193 NS</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Table 3 The insulin/histamine ratios and comparison between the ratios of the unoperated group with the ratios of the other groups

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>No</th>
<th>Mean ratio</th>
<th>95% tolerance limits</th>
<th>Test of postvagotomy groups against unoperated groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unoperated patients</td>
<td>81</td>
<td>0.64</td>
<td>1.31</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>All postvagotomy patients</td>
<td>81</td>
<td>0.48</td>
<td>0.92</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with recurrent ulcer</td>
<td>25</td>
<td>0.46</td>
<td>0.92</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with adequate vagotomy</td>
<td>29</td>
<td>0.41</td>
<td>1.06</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

significantly higher (Table 4).

None of the results already presented was altered when the raw data of acid outputs were used instead of V_G.

Discussion

FINDINGS IN UNOPERATED PATIENTS

Before vagotomy insulin produced a significantly smaller response of gastric secretion than did histamine. In occasional subjects the ratio of the responses varied widely from the logarithmic mean of 0.7, perhaps because of the difficulty in measuring gastric secretion accurately. Such variation in small numbers of observations might easily have influenced the results of earlier workers, especially when it is remembered that they had used histamine or pentagastrin in doses or by routes that must have produced sub-maximal responses. Corrections for pyloric losses and duodenogastric reflux do not appear to have made a significant contribution in that the results were not altered by calculations from raw data in the conventional manner.

It might be argued that this lesser response to a single injection of insulin was an artefact due to the rise and fall of secretion during the half to two hour period in contrast with the true plateau of maximal secretion with a continuous infusion of histamine. The response, however, to a single injection of histamine is about 90% of the response obtained to a histamine infusion8 that is, only 10% less, so that this factor is unlikely to account for the whole of the
30% difference found between the responses to the two secretagogues. Moreover, continuous intravenous infusion of insulin does not evoke a greater secretion than a single injection as used in this study.

Another possible explanation for the lesser response to insulin is that its inhibitory effect in the first half hour may continue during the subsequent period when hypoglycaemia is provoking secretion. This inhibitory effect, however, has been measured and is too small (about 20 ml/h) to account for the difference. In addition, sham feeding in humans produces the same as, or even less secretion than insulin. Thus the difference between insulin- and histamine-stimulated secretion is a real phenomenon and not an artefact produced by the dual stimulatory and inhibitory effects of insulin.

**EFFECTS OF VAGOTOMY**

One of the problems of assessing the effect of surgical vagotomy on patients is to decide whether the vagotomy has been adequate. Therefore we have looked at the postvagotomy results not only in terms of the whole group of 81 patients after vagotomy, but also in terms of two specially selected groups; one in which we were as sure as possible that vagotomy had been adequate according to criteria previously described, and one in which we were as sure as possible that vagotomy was inadequate because a recurrent peptic ulcer had been diagnosed. The assumption underlying the choice of this latter group, namely that the predominant cause of recurrent ulceration after vagotomy is inadequacy of the vagotomy, is well documented.

The ratio of the responses to insulin and histamine averaged about 0.7 before vagotomy and 0.4 after vagotomy, both in the inadequate and adequate vagotomy groups. The reason for the reduction in this ratio was explained by the numerical differences between insulin and histamine responses. The differences after vagotomy remained the same as before vagotomy, implying that the reduction in insulin-stimulated secretion was the same as the reduction in histamine-stimulated secretion. Clearly the subtraction of the same amount from the numerator and from the denominator of a fraction less than unity results in a smaller fraction. Furthermore, in the group with adequate vagotomy, insulin-stimulated secretion was really basal secretion and so the histamine response in this group did not differ significantly from the preoperative excess of the histamine response over the insulin response. For the same reason the preoperative correlation between the insulin and histamine responses was no longer present. On the other hand, in the inadequate group there was a correlation between insulin- and histamine-stimulated secretions because there still was some insulin-stimulated secretion.

**INTERPRETATION OF FINDINGS**

The conventional explanation of histamine/insulin relationships is that parietal cells have separate histamine- and acetyl choline-receptors. Little attention seems to have been paid to explaining the smaller response to acetyl choline (via insulin) than to histamine. The effect of vagotomy and of parasympatholytic drugs in reducing the response to histamine is explained by the sensitisation hypothesis that the histamine-receptor is only partially stimulated by histamine if there is no background stimulation of the acetyl choline-receptor, but that in the presence of such background stimulation the acetyl choline-receptor interacts with the histamine-receptor to produce maximal sensitivity in the latter, and maximal secretory response is achieved.

The details of any such explanation depend on whether the parietal cell is capable of a graded secretory response to graded stimulation or whether its response is all-or-none according to whether a threshold of stimulation has or has not been exceeded. Both possibilities are further explored below in the light of our findings in this study. See also the mathematical appendix.
ALL-OR-NONE RESPONSE
Maximal secretory rate represents the output of all the parietal cells. The response of the optimal acetyl choline stimulus is submaximal, as only a proportion (7/10) of the parietal cells are responding. Thus 3/10 of parietal cells cannot be stimulated by insulin, and can be considered to lack acetyl choline-receptors.

The crucial finding of the present paper is that, after adequate vagotomy, the response to histamine is quantitatively similar to that produced by only 3/10 of the parietal cells. According to the conventional hypothesis, in the presence of vagal innervation only 3/10 of the parietal cells are sensitive enough to respond to histamine, but in the presence of vagal innervation not only those 3/10 but also the remaining 7/10 are sensitive enough to respond. This hypothesis does not explain the apparent coincidence that the difference between pre- and postvagotomy histamine responses is quantitatively the same as the prevagotomy insulin response.

It seems simpler to propose that the value 3/10 is not a coincidence, and that the 3/10 of parietal cells that respond to histamine despite vagal denervation are the same cells that do not have acetyl choline-receptors. In other words, there are two types of parietal cells, 7/10 with acetyl choline-receptors and 3/10 with pure histamine-receptors. The fact that in the presence of the vagus all the cells respond to histamine suggests that histamine has an action on the 7/10 of cells with acetyl choline-receptors (provided that vagal innervation is intact) as well as on the 3/10 cells for which vagal innervation is unnecessary.

GRADED RESPONSE
In this version, maximal secretory rate represents the maximal response of all parietal cells, and the submaximal response to acetyl choline (7/10) represents a 7/10 maximal response from all parietal cells. All parietal cells thus have an acetyl choline-receptor. By the same token, all have a histamine receptor which in the absence of the vagus is stimulated by histamine to only 3/10 maximal secretion. Once again, the conventional view point is that it is coincidence that the prevagotomy insulin response and the postvagotomy histamine response add up to the prevagotomy histamine response. If vagal innervation is intact, the acetyl choline-receptor interacts with the histamine receptor to make it more responsive to histamine – by 7/10 of maximal secretion. Once again, it is a coincidence that the sensitisation is quantitatively the same as the maximal response of the acetyl choline-receptors to insulin.

We suggest that a simpler explanation is that the maximal secretory response of the parietal cell is the sum of the responses of the pure histamine-receptor to histamine and of the acetyl choline-receptor to histamine provided that vagal innervation is intact.

CHOICE BETWEEN SENSITISATION AND SUMMATION MODELS
Our data do not permit us to distinguish between these models. Summation, however, accounts for the equivalence between the vagal augmentation of the histamine response and the vagal response itself, while sensitisation leaves this equivalence unexplained as a coincidence. We therefore prefer summation to sensitisation.

CHOICE BETWEEN GRADED-STIMULATION AND ALL-OR-NONE MODELS
Again, we cannot critically distinguish between these as both fit the facts. By analogy with other effector cells, however, (such as muscle and nerve) we think the all-or-none model to be intrinsically more likely.

OUR PROPOSAL
We therefore propose that there are two types of parietal cells, 'H' and 'I' cells: only the 'I' cells respond to vagal stimulation, only the 'H' cells respond to histamine in the absence of the vagus, but the 'I' cells when vagally innervated can also respond to histamine.

We appreciate that this hypothesis is new – for example, it proposes that far from histamine being the final pathway for secretagogues acting on parietal cells, seven-tenths of the effect of histamine is via the final pathway of acetyl choline, that the number of observations is relatively small and that the quantitative relationships on which our argument is based are very approximate, with many large deviations in individual studies. Nevertheless, the hypothesis does at least seem to explain all the known facts (sensitisation never attempted to explain the smaller response to insulin compared with that to histamine) and we tentatively put it forward as a basis for future investigation.

This study is based on a paper presented to the British Society of Gastroenterology, Reading, September 1980.

Mathematical appendix
The findings of the present work may be summarised thus:
1 Before vagotomy, insulin-stimulated secretion, I₁
is about 70% of histamine-stimulated secretion, \( H_1 \).
\[
I_1 = 0.7 \times H_1 \quad \text{Equation 1}
\]

2 After inadequate vagotomy, the difference between histamine-stimulated secretion, \( H_2 \), and insulin-stimulated secretion, \( I_2 \), is the same as before operation.
\[
H_2 - I_2 = H_1 - I_1 \quad \text{Equation 2}
\]

3 After adequate vagotomy, insulin-stimulated secretion is so small as to be indistinguishable from basal; as a special case of equation 2, therefore, histamine-stimulated secretion, \( H_3 \), is the same as the prevagotomy histamine/insulin difference.
\[
H_3 = H_1 - I_1 \quad \text{Equation 3}
\]

If histamine stimulated secretion in the presence of full vagal innervation, \( H_1 \), is greater than in the absence of the vagus, \( H_3 \), because of a sensitisation of the parietal cells brought about by the intact vagus, in what quantitative terms should we express this effect? If the phenomenon was describable in terms of mass action, we might expect to express it as a multiplication factor \( H_1/H_3 \). On the assumption that the size of this factor was proportional to the number of vagal fibres innervating the parietal cells, an inadequate vagotomy would result in a shrinking of this multiplication factor. If a fraction, \( n \) (between zero and 1), of the vagal fibres were left intact, the multiplication factor would be reduced to \( n.H_1/H_3 \), so that \( H_2 = H_3 \times n.H_1/H_3 = n.H_1 \) while \( I_1 \) would presumably be reduced in the same proportion, and would therefore be \( n.I_1 \).

This means that the histamine/insulin difference after inadequate vagotomy is \( H_2 - I_2 = n.H_1 - n.I_1 = n(H_1 - I_1) \). In other words, we would expect the histamine/insulin difference to shrink as the efficacy of vagotomy increased, until with an adequate vagotomy (\( n=0 \)) there would be no difference.

These deductions are incompatible with equations 1–3 above. A sensitisation factor expressed as an addition, however, rather than a multiplication does fit the equations. On this model, the sensitisation produced by full vagal innervation is \( H_1 - H_3 \), which, when added to \( H_3 \), produces \( H_1 \). With a fraction, \( n \), of vagal fibres remaining the sensitisation is reduced to \( n(H_1 - H_3) \) so that \( H_2 \) is \( H_3 + n(H_1 - H_3) \). As before \( I_2 = n.I_1 \).

Therefore
\[
H_2 - I_2 = H_3 + n(H_1 - H_3) - n.I_1
\]
\[
= n(H_1 - I_1) + H_3 (1 - n)
\]
\[
(\text{but} \quad H_1 - I_1 = H_3)
\]
\[
= H_3 (n + 1 - n)
\]
\[
= H_3
\]

Thus the sensitisation model fits the facts, but only by making use of the observation embodied in equation 3. It makes use of the relationship, but does not explain it. Why should the sensitisation effect happen to be the same size as the response of the intact stomach to vagal stimulation?

Rewriting equation 3 as:
\[
H_1 = H_3 + I_1
\]

Equation 4 shows that histamine-stimulated secretion in the intact stomach seems to be the sum of two components – one produced by histamine in the vagally denervated stomach and one which is equivalent to the response of the acetyl choline-receptors in the intact stomach to vagal stimulation. This is the basis of the summation hypothesis proposed in the Discussion.

References

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Relationship between insulin- and histamine-stimulated gastric secretion before and after vagotomy.

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