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Effects of Truncal, Selective, and Highly Selective Vagotomy on Glucose Tolerance and Insulin Secretion in Patients with Duodenal Ulcer

C. S. HUMPHREY, J. R. W. DYKES, D. JOHNSTON

Part I—Effect of Vagotomy on Response to Oral Glucose

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Summary

An oral glucose tolerance test was performed in patients who had undergone truncal vagotomy and pyloroplasty, bilateral selective vagotomy and pyloroplasty, or highly selective vagotomy without a drainage procedure at least six months earlier. The results were compared with those from patients with chronic duodenal ulcer before operation. In all three groups of patients after vagotomy more rapid rates of rise of blood glucose and higher peak concentrations were observed than in patients who were tested before operation. These differences were statistically significant only in patients who had undergone truncal or selective vagotomy with pyloroplasty and were probably due to more rapid rates of gastric emptying after these operations.

Plasma insulin concentrations were lower after truncal vagotomy than after selective or highly selective vagotomy, the difference between truncal vagotomy and highly selective vagotomy being statistically significant. Truncal vagotomy resulted in a diminished insulin response to oral glucose, which could have been due to vagal denervation of the pancreas or, more probably, impaired release of small-bowel hormones which normally augment the pancreatic insulin response.

Introduction

Patients with chronic duodenal ulceration exhibit abnormal glucose tolerance and insulin secretion, which might be due to abnormal secretion of one or more small-bowel hormones.¹

University Department of Surgery, General Infirmary, Leeds 1

C. S. HUMPHREY, F.R.C.S., Surgical Registrar (Present appointment: Lecturer in Surgery, St. James's Hospital, Leeds 9)

D. JOHNSTON, M.D., F.R.C.S., Reader in Surgery

University Department of Chemical Pathology, General Infirmary, Leeds 1

J. R. W. DYKES, M.B., CH.B., Lecturer in Chemical Pathology

Vagotomy—whether truncal, selective, or highly selective—produces changes in the pattern of gastric emptying²⁻⁴ and thus might alter the disposal of a glucose meal. Vagotomy might also interfere with the synthesis, release, or action of gastrointestinal hormones which modify the insulin response to ingested carbohydrate.⁵⁻⁶ We therefore investigated the effect of vagotomy on carbohydrate metabolism. Three types of vagotomy were studied: truncal vagotomy and pyloroplasty, in which the stomach, small bowel and proximal large bowel, liver, biliary tract, and pancreas are vagally denervated; bilateral selective vagotomy and pyloroplasty, which denervates the entire stomach but preserves the parasympathetic innervation of the extragastric viscera via the hepatic and coeliac branches of the vagus; and highly selective vagotomy, which preserves the nerve supply to the gastric antrum as well and thus obviates the need for a drainage procedure.

Patients and Methods

Four groups of 15 patients were studied: patients with duodenal ulcer before operation, and patients who had undergone each of the three types of vagotomy at least six months earlier (table I). The group of patients suffering from chronic duodenal ulcer has been described.¹ The postoperative patients were all in good health, with no evidence of gastric retention, and eating a normal diet. All patients were within 10% of their ideal body weight, and none gave a history of diabetes. Each vagotomized patient had undergone an insulin test soon after operation which had shown that the vagotomy of the parietal cell mass was complete.⁷ In each case the diagnosis of duodenal ulceration had been confirmed at the time of operation.

PROCEDURE

The glucose tolerance test was carried out after the patient had fasted overnight. The patient drank the test meal (350 ml of a 25% solution of glucose) while standing. After the first 10 minutes the patient sat in a chair until the end of the two-hour test. Venous blood samples were withdrawn through an indwelling heparinized cannula before the test and at 10, 20, 30, 45, 60, 90, and 120 minutes.

Blood glucose concentrations were measured on an autoanalyzer by Morley *et al.*'s method,⁸ the coefficient of variation being 4.6% at a blood concentration of 5.83 mmol/l (105 mg/100 ml). Plasma immunoreactive insulin was measured in duplicate.⁹ Radioactive iodinated insulin and Oxoid membrane filters were supplied by the Radiochemical Centre, Amersham. The pre-precipitated antibody and standard human insulin were supplied by Burroughs Wellcome.

TABLE I—Details of Patients in each Group. Values are Means $\pm$ 1 S.E. of Mean

	No. of Patients	Sex (M. : F.)	Age (Years)	Height (m)	Weight (kg)	Time Since Operation (Months)
Duodenal ulcer	15	11 : 4	45.4 $\pm$ 3.4	1.71 $\pm$ 0.21	65.3 $\pm$ 2.7	
Truncal vagotomy	15	12 : 3	48.5 $\pm$ 3.6	1.71 $\pm$ 0.21	63.0 $\pm$ 2.2	12.9 $\pm$ 1.7
Selective vagotomy	15	12 : 3	42.9 $\pm$ 2.6	1.70 $\pm$ 0.20	62.3 $\pm$ 1.5	15.7 $\pm$ 1.9
Highly selective vagotomy	15	11 : 4	40.9 $\pm$ 2.9	1.70 $\pm$ 0.22	63.5 $\pm$ 2.5	10.3 $\pm$ 1.0

This assay method gave results with the following standard deviations: $\pm$ 2.92 m μ /l for 115 duplicate determinations in the range 0-49 m μ /l; $\pm$ 6.51 m μ /l for 64 determinations in the range 50-99 m μ /l; and $\pm$ 7.25 m μ /l for 55 determinations in the range 100-200 m μ /l. Samples with a plasma insulin concentration of more than 200 m μ /l were diluted and reassayed. With this exception all specimens from any one person were assayed in the same batch.

CALCULATIONS

Total insulin secretion in the two-hour period was estimated by computing the area beneath the plasma insulin curve from 0 to 120 minutes.¹⁰ Similarly the area beneath the blood glucose curve from 0 to 120 minutes was measured to give an index of glucose tolerance.¹¹ The ratio of these two areas—that is, insulin area:glucose area = insulinogenic index—relates insulin secretion to the glycaemic stimulus.¹²

The significance of differences between groups was calculated by Student's *t* test and verified by using the Mann-Whitney U test for nonparametric data.¹³

Results

Glucose.—The configurations of the curves of changes in blood glucose concentrations during the insulin test were similar in the three groups of vagotomized patients, with rapid rates of increase in blood glucose concentration, raised peak levels, and exaggerated falls toward hypoglycaemic levels. These changes were most definite after truncal vagotomy and pyloroplasty and least so after highly selective vagotomy, the differences between these two groups being statistically significant at 20, 30, and 45 minutes ($P < 0.02$, $P < 0.001$, $P < 0.01$ respectively). The glucose tolerance curve of patients who had undergone selective vagotomy and pyloroplasty was intermediate between those of the other two groups and not significantly different from either. The rates of rise of blood glucose concentration in the first 20 minutes of the test and the peak concentrations achieved were significantly greater after both truncal and selective vagotomy and pyloroplasty than in preoperative patients. After highly selective vagotomy these measurements did not differ significantly from those of patients before operation (table II).

Insulin.—The changes in plasma insulin concentration had the same pattern as the changes in blood glucose. The highest plasma insulin levels, however, were found after highly selective vagotomy and the lowest after truncal vagotomy. Significant differences between these two groups were found at 45 minutes ($P < 0.02$) and at 90 minutes ($P < 0.05$). Plasma insulin concentrations in the selective vagotomy group were once more intermediate, but resembled the pattern of the highly selective vagotomy group more than that of the truncal vagotomy group. After both selective and highly selective vagotomy the insulinogenic indices were significantly greater than after truncal vagotomy ($P < 0.01$).

Though insulin secretion in the two-hour period was greater after the selective types of vagotomy than after truncal vagotomy, the differences were not statistically significant. Glucose tolerance was

significantly better (as judged by the area beneath the blood glucose curve) after highly selective vagotomy than after truncal vagotomy (table II).

Discussion

Our results show that all three types of vagotomy lead to changes in the patterns of both glucose tolerance and insulin secretion compared with the patterns which are found before operation. Whereas blood glucose levels were significantly greater after truncal vagotomy and pyloroplasty than after highly selective vagotomy plasma insulin levels were significantly less.

An abnormal hyperglycaemic response to oral glucose has been described in patients with chronic duodenal ulcer who have not undergone operation.¹⁴⁻¹⁶ Our results indicate that the performance of a truncal vagotomy and pyloroplasty leads to further significant increases in both the rate of rise of blood glucose concentration and the peak concentration achieved. Selective vagotomy and pyloroplasty produced similar, though not so pronounced, changes. Highly selective vagotomy caused the least change in glucose tolerance. After all three types of vagotomy blood glucose levels fell rapidly in the latter part of the test, whereas in preoperative patients with duodenal ulcer a more diabetic form of blood glucose curve was seen.

Gastric surgery is a well-recognized cause of impaired glucose tolerance.

There have been many studies of glucose tolerance after both partial gastrectomy^{14-17, 20} and vagotomy with a drainage procedure.²¹⁻²³ Our own findings of a rapid rise of blood glucose concentration to an early peak of hyperglycaemia agree with these reports. Patients dumping after partial gastrectomy tend to have large decreases in plasma volume after the ingestion of hypertonic glucose.¹⁷⁻¹⁸ In such patients the maximum fall in plasma volume was found to be directly proportional to the rate of rise of blood sugar concentration in the first 10 minutes after the ingestion of the glucose meal. The reasons for these alterations in glucose metabolism after partial gastrectomy have been discussed by Holdsworth *et al.*²⁰ who suggested that the rapid rise and high peak concentration of glucose were due in large measure to an increased rate of gastric emptying and consequently an increased rate of intestinal absorption.

Gastric emptying of fluids and of food and barium is extremely rapid after vagotomy with a drainage procedure.²⁴⁻²⁶ and this is the likely cause of the changes in glucose tolerance which we found after both truncal and selective vagotomy with pyloroplasty. Similar changes in alcohol tolerance occur after vagotomy with a drainage procedure.²⁷ Gastric emptying of liquids after highly selective vagotomy, while more rapid than before operation, is significantly less rapid than after either truncal or selective vagotomy with pyloroplasty.^{3, 28-29} Thus the configuration of the glucose tolerance curve in patients after vagotomy is largely determined by the pattern of gastric emptying.

The high blood concentrations of glucose after truncal vagotomy

TABLE II—Details of Blood Glucose and Plasma Insulin in each Group. Values are Means $\pm$ 1 S.E. of Mean

	Blood Glucose			Plasma Insulin		
	Rate of Rise in First 20 Minutes (mmol l ⁻¹ min ⁻¹)	Peak Concentration (mmol/l)	Area Under Curve (0-120 min) (mmol l ⁻¹ min ⁻¹)	Peak Concentration (m μ /l)	Area Under Curve (0-120 min) (m μ l ⁻¹ min ⁻¹)	Insulinogenic Index
Duodenal ulcer	0.124 $\pm$ 0.013	9.05 $\pm$ 0.48	360.97 $\pm$ 38.35	130.7 $\pm$ 11.3	7638.1 $\pm$ 856.3	1.50 $\pm$ 0.28
Truncal vagotomy	0.247 $\pm$ 0.021	12.02 $\pm$ 0.54	391.37 $\pm$ 48.22	144.1 $\pm$ 14.8	6524.1 $\pm$ 755.2	0.97 $\pm$ 0.09
Selective vagotomy	0.210 $\pm$ 0.017	10.14 $\pm$ 0.64	327.85 $\pm$ 34.96	179.8 $\pm$ 17.7	7950.7 $\pm$ 787.9	1.89 $\pm$ 0.27
Highly selective vagotomy	0.167 $\pm$ 0.024	8.94 $\pm$ 0.73	265.85 $\pm$ 33.57	189.3 $\pm$ 17.3	9157.0 $\pm$ 886.7	3.22 $\pm$ 0.83

Conversion: SI to Traditional Units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

and pyloroplasty were not matched by a correspondingly large insulin response. Indeed, the reverse was true: whereas blood glucose concentrations after truncal vagotomy and pyloroplasty were significantly greater than after highly selective vagotomy, the insulin response to oral glucose, as judged by the insulinogenic index, was significantly less. The insulin response was also significantly less after truncal vagotomy than after selective vagotomy. The reason for this difference in insulin secretion is not clear. The similarity of the plasma insulin curves after selective and highly selective vagotomy suggests that vagal denervation of the small bowel and pancreas may be responsible. The lower insulin levels after truncal vagotomy could be due to direct vagal denervation of the pancreas or impaired release of gut hormones which augment the insulin response to an oral glucose load.⁵ The latter explanation is the more likely because of the discovery that the administration of atropine reduced the insulin response to both oral and intraduodenal glucose but not to glucose given intravenously.³⁰

Thus we formulated the hypothesis that the smaller insulin response which we found after truncal vagotomy than after selective or highly selective vagotomy was due to vagal denervation of the small intestine and that this in turn led to impaired release of a gastrointestinal hormone or hormones which are necessary for the optimal release of insulin. To test this hypothesis we compared the responses to oral and intravenous glucose after the three types of vagotomy. The results are presented in part II of this paper.

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Part II—Comparison of Responses to Oral and Intravenous Glucose

Summary

Paired oral and intravenous glucose tolerance tests were carried out in patients who had undergone truncal vagotomy and pyloroplasty, selective vagotomy and pyloroplasty, or highly selective vagotomy at least six months earlier. Intravenous glucose tolerance was similar in all three groups. Oral glucose elicited significantly higher concentrations of plasma insulin in patients who had undergone selective and highly selective vagotomy than in those treated by truncal vagotomy. When the same amount of glucose was given intravenously, however, plasma insulin concentrations were similar in all three groups of patients. The insulin secreted in response to intravenous glucose expressed as a percentage of that secreted in response to oral glucose was 112% for truncal vagotomy, 51% for selective vagotomy, and 52% for highly selective vagotomy. Truncal vagotomy thus led to a diminished insulin response to oral glucose, which was probably due to impaired release of small-bowel hormones.

Introduction

Our results in part I showed that truncal vagotomy results in diminished secretion of insulin in response to oral glucose. Is this impaired insulin secretion a direct effect of vagal denervation of the pancreas, or is it mediated indirectly through impaired release by the small intestine of hormones which normally stimulate the release of insulin? To try to define the possible role of small-bowel hormones in the impaired secretion of insulin after truncal vagotomy we gave patients the same amount of glucose orally on one occasion and intravenously on another. The patients had undergone either truncal vagotomy

and pyloroplasty, selective vagotomy and pyloroplasty, or highly selective vagotomy without a drainage procedure, as described in part I.

Patients and Methods

Eight patients from each vagotomy group agreed to have paired tests of intravenous and oral glucose tolerance. The two tests were carried out in random order, the second test being performed at least one week after the first. The patients were representative of the groups described in detail in part I. The oral glucose tolerance test was performed as described in part I. The intravenous glucose tolerance test was performed after an overnight fast. A solution of 350 ml of 25% glucose was infused at a constant rate into a peripheral vein over 25 minutes. Venous blood samples were withdrawn through an indwelling heparinized cannula before the infusion began and at 10, 20, 30, 45, 60, 75, 90, 105, and 120 minutes. Details of measurements of blood glucose concentrations¹ and plasma insulin concentrations² and the statistical methods used were given in part I.

Results

During the infusion of glucose blood glucose concentrations rose rapidly in all three groups of patients, reaching a peak at 20-30 minutes. The rate of increase was most rapid in patients who had undergone truncal vagotomy, whose mean blood glucose concentrations were significantly higher at 10 minutes (17.8 mmol/l (320 mg/100 ml)) and 20 minutes (26.6 mmol/l (480 mg/100 ml)) than those of patients who had undergone either selective vagotomy (13.9 mmol/l (250 mg/100 ml), $P<0.02$; and 17.8 mmol/l (320 mg/100 ml), $P<0.001$ respectively) or highly selective vagotomy (12.2 mmol/l (220 mg/100 ml), $P<0.01$; and 21.6 mmol/l (390 mg/100 ml), $P<0.01$). Thereafter blood glucose concentrations decreased rapidly in each group, and no other significant differences were found. The rate constant, K , for the disappearance of glucose from the blood