Effect of massive bowel resection on enteroinsular axis

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SUMMARY Pancreatic endocrine function was studied in 13 patients who had undergone massive bowel resection. The patients were divided into two groups: one month after operation (short-term group), and three or more months after operation (long-term group). Oral administration of glucose caused a persistent low insulin secretion in almost all the patients and the glucose tolerance curve showed a diabetic pattern in four. In contrast, the insulin response to intravenously infused arginine was impaired in the short-term group, but was at an approximately normal level in the long-term group. Pancreatic glucagon response to intravenous arginine, however, remained unchanged in both groups. Interruption of the enteroinsular axis as the result of massive bowel resection probably plays a major part in this discrepancy of the behaviour of insulin in the long-term group.

Oral administration of glucose produces a considerably greater rise in serum insulin levels than does intravenous administration of glucose (McIntyre *et al.*, 1964). This evidence led Unger and Eisentraut (1969) to advocate the concept of an enteroinsular axis in which some hormones in the intestinal mucosa regulate the secretion of the islet cells. Several kinds of insulinotrophic agents which might be responsible for this phenomenon have been proposed on the basis of their distribution in the intestine. Massive bowel resection may induce interruption of the enteroinsular axis which follows the dysfunction of the islet cells.

There are few reports in the literature on changes in islet cell function after intestinal resection. The present study was an attempt to compare the endocrine function of the pancreas in patients with massive bowel resection with that of normal volunteers and to discuss the effect of intestinal resection on the enteroinsular axis.

Methods

CONTROLS

Ten healthy, normal volunteers (five females, five males) ranging in age from 32 to 65 years (mean 49.8 years) served as controls. All were within 10% of their ideal body weight.

PATIENTS WITH MASSIVE BOWEL RESECTION

Thirteen patients (seven females, six males) ranging in age from 32 to 70 years (mean 53.6 years) were

investigated. All had undergone surgery after the diagnoses listed in Table 1. These patients were divided into the short-term and the long-term group according to the intervals after the operation. The former included six patients who had been operated on one month before and the latter included seven who had had surgery three or more months previously.

After an overnight fast, 50g glucose was given orally and venous blood samples were collected to determine plasma glucose and insulin before and 30, 60, 90, and 120 minutes after the oral glucose load. The insulinogenic index was determined by the ratio of increments of insulin over fasting levels at 30 minutes to those of blood glucose ($\Delta\text{IRI}/\Delta\text{BS}$ (30 min)). The output of insulin during the oral glucose tolerance test was calculated by measuring the area under each curve from fasting to 120 minutes ($\Sigma\Delta\text{IRI}$ (0— > 120 min)) and expressed arbitrarily in $\mu\text{U}/\text{ml}$. On another day, L-arginine in a dose of 30 g was infused during a period of 45 minutes and blood samples were collected to determine plasma insulin and glucagon before, and six, 10, 20, 30, 45, 60, and 90 minutes after the start of the infusion. The output of insulin and glucagon in response to arginine was also calculated by measuring the area under each curve from fasting to 90 minutes ($\Sigma\Delta\text{IRI}$ (0— > 90 min), $\Sigma\Delta\text{IRG}$ (0— > 90 min)) and expressed arbitrarily as $\mu\text{U}/\text{ml}$ and pg/ml respectively. The insulin-glucagon ratio in the fasting state was computed (Unger, 1971). The blood glucose concentration was determined by using an autoanalyser. Plasma insulin level was determined radioimmunologically using a CIS-kit

Table 1 Clinical features of patients with massive bowel resection

Case no.	Age (yr)	Sex	Body weight (kg)	Diagnosis	Part of small bowel resected	Length of small bowel remaining (m)	Interval since resection (months)
Short-term group							
1	41	f	45	Adhesions ileus	Ileum	2.0	1
2	65	m	51	Incarceration	Ileum	2.2	1
3	52	f	47	Adhesions ileus	Ileum	2.5	1
4	47	f	53	Strangulations ileus	Jejunum	1.8	1
5	62	m	67	Intestinal rupture	Jejunum	1.5	1
6	58	f	44	Adhesions ileus	~ileum Jejunum	1.5	1
Long-term group							
7	38	f	53	Adhesions ileus	Ileum	2.0	3
8	54	m	72	Intestinal rupture	Jejunum	1.5	12
9	64	m	65	Incarceration	~ileum		
10	52	f	42	Adhesions ileus	Ileum	2.2	4
11	70	m	55	Adhesions ileus	Jejunum	2.5	5
12	62	m	60	Intestinal rupture	Ileum	1.5	156
					Jejunum	1.5	6
13	32	f	50	Intestinal rupture	~ileum Jejunum	2.0	3

and plasma glucagon with 30-K antibody by the method of Unger and his colleagues (Unger *et al.*, 1967). The glucose and arginine tests in the normal volunteers were repeated twice at several intervals, respectively, and the average of two readings was adopted.

Results

ORAL GLUCOSE TOLERANCE TEST

Table 2 summarises the results of the glucose tolerance test in the control, the short-term, and the long-term group. The fasting blood glucose remained at normal levels in all but one of the long-term group. After the glucose load, a diabetic curve (American Diabetes Association, 1969) was observed in two patients of both short-term and long-term groups. The remaining four of the short-term group and five

Fig. 1 Insulin secretion after oral glucose (mean $\pm$ SE).

of the long-term group were within normal limits. The secretion of insulin in this test was, as shown in Fig. 1, reduced both in the short-term and long-

Table 2 Plasma glucose levels in oral glucose and insulinogenic index (mean $\pm$ SE)

Case no.	Blood glucose levels (mmol/l)			Insulinogenic index (Δ IRI/ Δ BS (30 min))
Control group	4.60 $\pm$ 0.143	6.54 $\pm$ 0.340	5.04 $\pm$ 0.399	19.84 $\pm$ 1.311
Short-term group				
1	5.2	8.6	8.6	5.92
2	4.6	8.7	7.4	4.82
3	4.5	9.9	8.5	5.00
4	4.9	7.4	6.7	5.99
5	4.4	6.4	7.5	3.73
6	5.3	10.3	9.6	2.95
Mean	4.82 $\pm$ 0.154	8.55 $\pm$ 0.602	8.05 $\pm$ 0.426	4.662 $\pm$ 0.496
Long-term group				
7	3.8	6.6	5.9	3.82
8	4.5	8.1	5.9	10.91
9	3.4	9.3	9.4	0.23
10	5.9	10.6	8.4	4.10
11	4.6	8.1	5.9	1.13
12	5.1	7.5	6.1	4.77
13	5.3	8.4	7.8	4.82
Mean	4.66 $\pm$ 0.327	8.37 $\pm$ 0.485	7.06 $\pm$ 0.552	4.248 $\pm$ 1.440

Fig. 2 Insulin response to intravenous arginine (mean $\pm$ SE).

term group. The insulinogenic index in the control group was 19.84 ± 1.311 , which decreased significantly to 4.662 ± 0.496 ($P < 0.001$) and 4.248 ± 1.440 ($P < 0.001$) in the short-term and the long-term group. The output of insulin during a 120 minute period after oral glucose load ($\Sigma \Delta \text{IRI}(0 - > 120 \text{ min})$) was $2599 \pm 211.8 \mu\text{U/ml}$ in the control group. It decreased to $1477 \pm 229.6 \mu\text{U/ml}$ ($P < 0.005$) in the short-term group and remained impaired ($1351 \pm 288.8 \mu\text{U/ml}$, $P < 0.005$) even in the long-term group.

INTRAVENOUS ARGININE LOAD

Insulin response

As shown in Fig. 2, the insulin response to infused arginine was reduced in the short-term group but was almost to the level of the controls in the long-term group. The output of insulin in response to intravenous arginine ($\Sigma \Delta \text{IRI}(0 - > 90 \text{ min})$) in the control group was $1294 \pm 142.5 \mu\text{U/ml}$, which de-

Fig. 3 Pancreatic glucagon response to intravenous arginine (mean $\pm$ SE).

creased to $421 \pm 157.0 \mu\text{U/ml}$ ($P < 0.005$) in the short-term group, but there was no statistical difference ($893 \pm 141.3 \mu\text{U/ml}$, $0.1 < P < 0.5$) in the long-term group. Thus, insulin response to arginine was impaired significantly only in the short-term group.

PANCREATIC GLUCAGON RESPONSE

The response of glucagon to intravenous arginine was much the same as in the control group in both the short- and long-term groups (Fig. 3).

The output of glucagon in response to the stimulant ($\Sigma \Delta \text{IRG}(0 - > 90 \text{ min})$) in the controls, the short-term group and the long-term group was 15471 ± 1412.2 , 18520 ± 2488.9 and $16549 \pm 6281.8 \text{ pg/ml}$, respectively. There were no statistical differences among these three groups.

Insulin glucagon ratio in the fasting state was 2.148 ± 0.446 in the controls, but decreased significantly to 1.168 ± 0.427 ($P < 0.05$) in the short-term group. The ratio in the long-term group was 2.060 ± 0.550 , which was not statistically different from that in the controls.

Discussion

We found that plasma insulin response to oral glucose was impaired not only one month after but also more than three months after massive bowel resection. Similarly, insulin response to infused arginine was also reduced one month after the intestinal resection. The response at three months or more was much the same as in the controls. Malnutrition inevitably occurs after massive bowel resection, and is not compensated far until about one month after operation (Althausen *et al.*, 1950). On the other hand, release of glucagon and insulin in response to infused arginine participates in glucose production and protein synthesis in the liver (Cherrington *et al.*, 1974). Therefore, it is reasonable that the low insulin release mediated by arginine seen in the short-term group might be the result of post-operative catabolism and malabsorption of the protein. Unger (1971) also pointed out the low molar ratio of two pancreatic hormones in catabolic illness. In fact, the insulin glucagon ratio in our patients in the fasting state decreased only in the early stage after the operation.

The impaired glucose tolerance in two patients with massive bowel resection improved gradually with time. The blood glucose curve was quite normal by six months after the resection. These occurrences are the result of enhanced glucose absorption by the intestinal remnants (Dowling and Booth, 1966; Weinstein *et al.*, 1969). In the present study, glucose tolerance was disturbed in only four of 13 patients

with massive intestinal resection, while the insulinogenic index in oral glucose load was impaired in almost all the patients, including one who had undergone surgery 10 years before. Thus, the low insulin secretion in response to oral glucose is probably the result of impairment of insulin release from islet cells rather than of a disturbance in glucose absorption.

Wapnick and Jones (1972) reported that glucose tolerance after intestinal resection showed a marked decrease in insulin response to intravenously administered glucose, but not to oral glucose. They attributed this finding to a decrease in the fasting release of the alimentary insulinotropic agents, including gastrin, secretin, pancreozymin-cholecystokinin, and enteroglucagon. The discrepancy between these results and our present data may be due to the area and/or length of the small intestine which had been resected. As is well known, glucose and amino acids give rise to a greater release of insulin, when they are administered *via* the gastrointestinal tract than *via* the intravenous route (McIntyre *et al.*, 1964). Based on this evidence, the concept of an enteroinsular axis was proposed (Unger and Eisentraut, 1969) and the importance of enteric factors which regulate islet cell function was stressed. Our findings that insulin response to oral glucose remained suppressed even for a long time after resection, while the response to intravenously administered arginine returned to the control levels may be explained by the interruption of the enteroinsular axis as the result of resection of the small intestine.

In fact, arginine is considered to have a different mechanism of action compared with glucose. But even the mechanism of insulin release from β cell in response to intravenously administered glucose is not quite the same as in response to oral glucose. Our objective in this paper was to compare the behaviour of insulin *via* the enteroinsular axis with that of insulin *via* the non-enteroinsular axis. The chief reason for using arginine was to determine how pancreatic glucagon acts in the short bowel syndrome.

In contrast with the obvious impairment of insulin release, normal secretion of pancreatic glucagon in arginine infusion was observed after intestinal resection. As presented in the bihormonal disorder hypothesis, there is an absolute or relative hypersecretion of glucagon in addition to an absolute or relative insulin deficiency in diabetes mellitus (Unger, 1971). In our results, hypersecretion of glucagon relative to insulin in response to intravenous arginine was found in the short-term group, but not in the long-term group. The lowered insulin release to arginine in the early postoperative period can be

explained by catabolism after operation: this relative hyperglucagonemia to arginine is manifested in the postoperative catabolic state. Meanwhile, low insulin secretion in response to oral glucose was observed in both short- and long-term groups. Accordingly, it can be stated that relative hypersecretion of glucagon remains after intestinal resection, when insulin glucagon ratio is calculated against the ratio of insulin in glucose to glucagon in arginine. This diabetic state induced by a relative hyperglucagonemia may be the result of loss of the intestinal 'signal' in the mechanism of insulin release in β cells.

Reduction or loss of certain insulinotropic hormones is responsible for the lowered insulin secretion after bowel resection. According to recent literature, secretin (Unger *et al.*, 1967; Kraegen *et al.*, 1970), pancreozymin-cholecystokinin (Unger *et al.*, 1967), enteroglucagon (Unger *et al.*, 1968), gastrin (Unger *et al.*, 1967), gastric inhibitory polypeptide (Dupre *et al.*, 1973) are all regarded as insulinotropic hormones in the gastrointestinal tract. Among them, release of a gastric inhibitory polypeptide has been described after oral ingestion of glucose (Brown *et al.*, 1975). This hormone is apparently located throughout the small intestine in man (Thomas *et al.*, 1977). Recently, the lower response of gastric inhibitory polypeptide to a test meal was found in patients with coeliac disease (Creutzfeldt *et al.*, 1976), and this has been attributed to the numerical reduction of GIP cells in the small intestine in coeliac disease. It may be that after intestinal resection the absolute number of GIP cells decreases in the short bowel syndrome and that the lack of stimulation by this hormone results in a low insulin release.

Another factor responsible for the impaired insulin secretion after bowel resection may be enteroglucagon. Enteroglucagon is found throughout the small intestine, particularly in the lower area (Bloom, 1974) and is released after glucose ingestion (Unger *et al.*, 1968). The secretion of enteroglucagon was found to be suppressed after massive intestinal resection in dogs (Barros D'Sa and Buchanan, 1977).

A decrease in the number of intestinal endocrine cells may result in an interruption of the enteroinsular axis, which results in a low insulin secretion in short bowel syndrome.

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