Plasma insulin response to oral carbohydrate in patients with glucose and lactose malabsorption

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SUMMARY Plasma insulin levels were determined following oral glucose in 12 patients with adult coeliac disease, after oral lactose in four patients with alactasia, and in age-matched control subjects.

In coeliac patients the insulin response was greater than expected from the small rise in blood sugar, and no correlation was found between plasma insulin and sugar levels at any period during the test. The separation of the plasma insulin curve from the blood sugar curve after glucose is in keeping with the concept that a factor responsible for stimulating insulin secretion is released from the gut during or after absorption of glucose.

In patients with selective lactose malabsorption (alactasia) administration of lactose by mouth failed to elicit any insulin response, indicating that the insulin-releasing effect of the bowel is not activated merely by the presence of intraluminal carbohydrate.

The availability of a sensitive immunoassay has led to the recognition that the secretion of insulin *in vivo* is closely dependent on the blood sugar level (Yalow and Berson, 1960) and studies with isolated pancreas preparations have shown a similar increase in insulin output when the glucose concentration in the incubating medium is raised (Malaisse, Malaisse-Lagae, and Wright, 1967).

Increase in blood glucose above a threshold level was considered to be the only important physiological stimulus for insulin release (Field, 1964) until the demonstration by McIntyre, Holdsworth, and Turner (1964) that the infusion of glucose into the jejunum produced a greater rise in insulin than an equivalent amount infused intravenously indicated that factors other than the blood glucose level were concerned in the insulin response following oral glucose.

Absorption of glucose may release a humoral substance from the bowel which then acts, together with the increase in blood glucose, in

stimulating release of insulin from islet cells (McIntyre *et al.*, 1964). An insulinotropic effect has been attributed to various gastrointestinal hormones (see the reviews by Holdsworth, 1969, and Mayhew, Wright, and Ashmore, 1969) but the mechanisms involved in gut-mediated insulin release are not clearly understood. We have approached this problem by studying the plasma insulin response to oral glucose in patients with adult coeliac disease (with subtotal villous atrophy and malabsorption of glucose) and to the disaccharide lactose in patients with selective lactose malabsorption (alactasia).

Patients and Methods

COELIAC DISEASE

Twelve patients (five male and seven female), with a mean age of 42 years, who weighed on average 10% less than ideal for height and sex, were studied. Four patients had started a gluten-

Received for publication 6 April 1970.

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free diet, while the remaining eight were studied before gluten withdrawal. Jejunal biopsy at the time of study showed subtotal atrophy in all patients.

Standard 50g oral glucose tolerance tests were performed after an overnight fast. Venous blood was taken for blood sugar and insulin estimations were made at 0, 15, 30, 60, 90, and 120 minutes. The results were compared with those from 12 age-matched controls who were all within 10% of ideal body weight.

In seven coeliac patients and seven control patients an intravenous glucose tolerance test was also performed. Venous blood was removed while the patients were fasting and at 10, 20, 30, 40, 50, and 60 minutes after 25g intravenous glucose.

ALACTASIA

Four patients (all male) with a mean age of 35 years were studied. The diagnosis of alactasia had been made on a history of milk intolerance, confirmed by lactose tolerance tests and jejunal lactase activity of under 0.3 units/g mucosa (lower limit of normal lactase activity for our laboratory 1.0 unit/g mucosa) (Ferguson and Maxwell, 1967). In each case small-bowel histology was normal. In these patients venous blood was taken at 0, 15, 30, 60, 90, and 120 minutes after 100g oral lactose and results were compared with four age-matched normal control subjects. None of the patients nor control subjects studied were diabetic.

Blood sugar was measured as total reducing substances on a Technicon AutoAnalyzer. Plasma insulin was assayed by the immunoprecipitation technique of Hales and Randle (1963), using standards and antisera previously described (Buchanan and McKiddie, 1967a).

Results

INSULIN RESPONSE TO GLUCOSE

The effect of intravenous glucose is shown in Fig. 1, and demonstrates a virtually identical sugar and plasma insulin response in control and coeliac groups. There is thus no evidence for a delayed or impaired pancreatic response to the stimulus of hyperglycaemia in the coeliacs.

In control subjects the sugar and insulin curves following oral glucose closely parallel each other (Fig. 2). In the coeliac patients the sugar curve is much flatter (mean maximal rise of only 11 mg%) consistent with glucose malabsorption, the insulin rise is slower than in the controls, with a delayed peak, and the curve does not parallel the sugar curve. Coeliac patients were found to have a significantly lower sugar level at 15 minutes and 30 minutes after oral glucose than controls ($P < 0.01$), but a statistically signifi-

Fig. 1 Sugar and insulin response to intravenous glucose (25g) in seven control subjects (left) and seven coeliac patients (right). (Here and in Figures 2 and 4, ●—● denotes plasma insulin and × --- × blood sugar.)

Fig. 2 Sugar and insulin response to oral glucose (50g) in 12 control subjects (left) and 12 coeliac patients (right).

Fig. 3 Sugar and insulin areas after oral glucose in control subjects (black area) and coeliac patients (dotted area).

Fig. 4 Sugar and insulin response to oral lactose (100g) in control subjects (left) and patients with alactasia (right).

ficant difference in insulin levels occurred only at 15 minutes following oral glucose ($p < 0.05$).

The areas below the sugar and plasma insulin response curves (calculated as mg/min/100 ml for sugar and microunits/min/ml for insulin) give some measure of sugar absorption and plasma insulin secretion (Kalkhoff, Schalch, Walker, Beck, Kipnis, and Daughaday, 1964; Perley and Kipnis, 1965). The sugar and insulin areas expressed as percentages of control values are shown in Figure 3. It can be seen that although the overall insulin response in coeliacs is decreased to 65% of the control value, this is out of proportion to the sugar response which is only 22% of the response in control patients.

A significant positive correlation was found between sugar and insulin values in control subjects at 60 minutes ($r = 0.67$), 90 minutes ($r = 0.70$), and 120 minutes ($r = 0.83$) after oral glucose. In the coeliac patients on the other hand, where little rise in blood sugar occurs, no correlation was found between sugar and insulin levels at any time during the test period.

INSULIN RESPONSE TO LACTOSE

Figure 4 shows the effect of oral lactose on the sugar and insulin response in patients with alactasia, and in the control group. In the alactasia group the sugar curve is flat (lactose malabsorption) and there was no insulin response, while in controls there is a normal rise in sugar and insulin levels after oral lactose.

Discussion

A positive correlation between sugar and insulin levels has been found in the latter part of the oral glucose tolerance test in normal control subjects in this and other studies (Buchanan and McKiddie, 1967b; Martin, Pearson, and Stocks, 1968). These findings are consistent with the view that

insulin secretion at this stage is determined by a direct effect of the elevated blood sugar on islet cells, as has been shown with isolated pancreas preparations (Malaisse *et al*, 1967). On the other hand the absence of correlation between these variables in the first hour after glucose ingestion suggests that insulin secretion during the initial period of the glucose test may be largely the result of a factor or factors other than the blood sugar level, and an insulin release mechanism mediated by the gut may provide the explanation for this early insulin response.

In coeliac patients where glucose absorption is greatly diminished (Holdsworth and Dawson, 1965) and the increment in blood sugar above fasting levels is small, no correlation is found at any stage in the test between sugar and insulin values. It is interesting to speculate whether the insulinotropic effect of the bowel might be the major factor in determining insulin secretion throughout the test period in these patients with glucose malabsorption.

These studies provide further evidence for the existence of an insulin-releasing effect by the alimentary tract. The site of release of the insulin-stimulating factor remains unknown, but it is unlikely to originate from the liver or portal circulation (McIntyre, Turner, and Holdsworth, 1968; Holdsworth, 1969).

We have shown that the stimulus to the release of an insulinotropic factor does not depend merely on mucosal contact or indirect changes (such as in pH, motility, or osmotic pressure) evoked by the passage of carbohydrate into the lumen of the small bowel, for the presence of unabsorbed lactose in the gut of lactase-deficient patients did not produce a rise in plasma insulin. This suggests that it may be the onset of monosaccharide absorption which stimulates the bowel-mediated release of insulin after oral carbohydrate. As there is experimental evidence that insulin can enhance the absorption of glucose from the small intestine *in vitro* (Love and Canavan, 1968) such an interrelationship could provide a feedback system for facilitating glucose absorption.

We thank Professor E. M. McGirr and Dr A. H. Imrie for their encouragement and support, and are grateful for Miss Isobel Hunter's expert technical assistance. One of us, J.D.M., was in receipt of a McIntyre research scholarship from the Royal Infirmary, Glasgow.

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