SERUM LEVELS OF IMMUNOREACTIVE GASTRIC INHIBITORY POLYPEPTIDE AND INSULIN IN URAEMIC PATIENTS

D Matthaei, R Ebert, P Schauder, H Frerichs, W Creutzfeldt, F Scheler

University Hospital, Göttingen, FRG

Introduction

The changes in glucose metabolism in uraemia have been attributed to altered secretion and metabolism of insulin, glucagon, HGH, PTH\(^1\), and the presence of basic peptides that form complexes with insulin\(^2\).

The hormone gastric inhibitory polypeptide (GIP)\(^3\) is released by the intestinal mucosa and has a potent dose dependent insulinotropic effect in vivo and in vitro. GIP is supposed to be a major component of the enteroinsular axis and is predominantly released in response to oral ingestion of glucose, fat and amino acids. It has been characterised as a straight chain polypeptide with 43 amino acids and a calculated molecular weight of 5105.

As the kidney is involved in the metabolism and excretion of many peptides, it is of interest to know whether the secretory pattern of GIP is disturbed in chronically uraemic patients. The present investigation was performed to obtain information on immunoreactive GIP (IR-GIP) levels in uraemia in the fasting state and after oral glucose load.

Materials and Methods

The studies were done in 8 healthy volunteers, 8 unselected patients on haemodialysis treatment and 10 patients with different degrees of compensated renal failure. The patients on haemodialysis treatment were dialysed three times a week for seven hours with a AB-Gambro-lundia-major haemodialyser.

After an overnight fast and at least 45 minutes rest in the supine position an indwelling cannula was inserted into the antecubital vein of one forearm for blood sampling. In the chronically uraemic patients the test was performed after a dialysis-free interval of 2 days. In the patients with compensated renal failure a single fasting sample was taken. An oral glucose load (100 g) was given in the normal controls and in the patients on haemodialysis treatment after taking the fasting level. Blood samples were taken after ingestion of glucose, at 30-minute intervals for five hours. The samples were immediately
placed on ice and centrifuged at 4° C. Afterwards they were deep frozen and stored at 20° until assayed. Blood glucose was measured in duplicate on each sample by the glucose oxidase method after separating the serum.

IR-GIP and immunoreactive insulin (IRI) were determined in duplicate on each sample within four weeks of the test. Serum IR-Insulin was determined using human insulin as a standard4. Serum IR-GIP was measured using the technique of Kuzio et al5 with a new antibody raised in rabbits. Results are expressed as the mean ± SEM.

Results

Serum fasting levels of IR-GIP (Figure 1) are elevated nearly fourfold in compensated renal failure and nearly sevenfold in patients on haemodialysis treatment (normal controls 190 ± 49 pg/ml; compensated renal failure 729 ± 136 pg/ml; dialysis patients 1302 ± 179 pg/ml). There was no significant correlation between creatinine and fasting levels of IR-GIP.

The stimulated values of IR-GIP reach a higher level in uraemic patients (Figure 2). After stimulation with oral glucose IR-GIP reaches its peak level (704 ± 72 pg/ml) at 90 minutes in normal controls and returns to basal levels after 210 minutes. In uraemic patients there is a faster rise in the first 30 minutes than in controls and IR-GIP reaches its peak level at 120 minutes (2300 ± 177 pg/ml). The subsequent decrease of IR-GIP is delayed and does not reach basal levels in uraemic patients, even five hours after glucose ingestion.

The course of IR-Insulin (Figure 3) after oral glucose load in normal controls shows a rapid rise to a first peak level at 30 minutes (69 ± 10 μU/ml) and a second peak at 150 minutes (63 ± 9 μU/ml). IR-Insulin reaches basal levels in normal controls at 270 minutes. In the uraemic patients mean IR-Insulin levels show a delayed rise reaching a peak level at 120 minutes (57 ± 8 μU/ml). The fall of IR-Insulin in the uraemic patients is slower than in the controls and does not reach basal fasting levels within the test period.

Blood glucose (Figure 4) falls continuously in normal controls after an initial peak level (157 ± 12 mg/100 ml) at 30 minutes. In normal controls blood glucose reaches basal fasting levels 270 minutes after the oral glucose load. After prolonged elevation up to 120 minutes blood glucose falls continuously until 270 minutes in the uraemic patients. At this time mean blood glucose reaches values (60 ± 6 mg/100 ml) below the basal fasting value in uraemic patients (83 ± 3 mg/100 ml).

Two oral glucose tolerance tests in the uraemic patients had to be discontinued at 210 and 240 minutes, because of severe signs of hypoglycaemia with blood glucose 40 and 45 mg/100 ml respectively. The glucose response to oral glucose was diabetic in these two patients. In three more uraemic patients mild signs of hypoglycaemia, such as hunger and restlessness, occurred between the third and fifth hour of the test. When the clinical signs of hypoglycaemia occurred, blood glucose had fallen below the initial fasting level in all uraemic patients.
Figure 1. Fasting values of Gastric Inhibitory Polypeptide in 8 normal controls, 10 patients with compensated renal failure (creatinine 1.7 ± 0.3 mg%) and 8 chronic uraemic patients
GASTRIC INHIBITORY POLYPEPTIDE

Figure 2. Stimulated values of IR-GIP in 8 normal controls and 8 chronic uraemic patients

[μU/ml] IR-INSULIN

Figure 3. Stimulated values of IR-Insulin in 8 normal controls and 8 chronic uraemic patients
The course of IR-Insulin, IR-GIP and blood glucose in one patient, whose test had to be discontinued due to severe signs of hypoglycaemia at 210 minutes, is shown in Figure 5. A continuous rise of IR-GIP to 2900 ng/ml at 120 minutes and elevated levels of blood glucose up to 120 minutes are accompanied by a subsequent rise in IR-Insulin until this time (68 µU/ml). The resulting fall in blood glucose reaches values of 45 and 40 mg/100 ml at 180 and 210 minutes. Severe cold, perspiration, mental disorder and tachycardia forced discontinuation of the test at this time, in this and one other uraemic patient.

In none of the normal control studies were clinical signs or blood glucose indicative of the occurrence of reactive hypoglycaemia after oral glucose load.

Discussion

Our data confirm that glucose tolerance is frequently impaired in uraemic patients. The elevated fasting levels of IR-GIP in patients with compensated renal failure and patients on chronic intermittent haemodialysis treatment are evidence that the kidney plays an important role in the metabolism of GIP. The stimulated values of GIP in eight normal controls and eight patients on intermittent haemodialysis treatment also suggest that there is a higher level of secretion of IR-GIP after oral glucose load with a delayed decrease of IR-GIP.
levels. This might indicate delayed metabolism of GIP, which may be responsible for the elevated fasting levels of this hormone in uraemia.

As GIP, a hormone that may enhance insulin response to oral glucose load, is retained in uraemia, this hormone might be involved in the altered glucose metabolism of uraemic patients. Further interpretation of the individual data in only 8 uraemic patients after oral glucose load should be made with caution. Many other factors probably affect the metabolism of glucose in uraemia. The frequent observation of mild hypoglycaemic signs and the observation of severe hypoglycaemic episodes after oral glucose load are of special interest. The reactive hypoglycaemia observed here may explain the hypoglycaemic episodes observed in uraemic patients.

The high fasting and stimulated levels of GIP and concomitant rise of IR-Insulin to late peak levels, as observed in two patients, may be responsible for the following hypoglycaemic episodes. But this remains speculative, until all the other factors affecting glucose tolerance in uraemia have been elucidated.

Acknowledgments

The authors wish to thank Mrs K Illmer, Mrs B Hillebrecht, Miss E Heuer and Mr K Hansmann for their technical assistance.
References

3 Brown, JC, Drysburgh, JR, Ross, SA and Dupré, J (1975) Recent Progr. Hormone Res. 31, 487
5 Kuzio, M, Drysburgh, JR, Malloy, KM and Brown, JC (1974) Gastroenterology, 66, 357

Open Discussion

DZURIK (Bratislava) Is the GIP really active?

MATTHAEI As concerns the specificity of the assay, our antibody has no cross-reactivity with other known polypeptides and there is no cross-reactivity with N-terminal fragments. Data from haemofiltration are indicative that it is the intact GIP molecule that is filtered and that it is present in the plasma of uraemics.

DRÜECKE (Paris) We have recently performed oral glucose tolerance tests before and after subtotal parathyroidectomy in 12 patients and we found, as you did, a diabetic or abnormal glucose disappearance curve. We cannot confirm your finding of a pathological insulin response to oral glucose loading, neither before or after the parathyroidectomy. Are the differences between your normal population and your renal insufficiency patients significant at any of the time points studied, and at what level?

MATTHAEI Only the 30 minute value was significant for the insulin levels. But you know that it is not useful to compare these values statistically. It seems more interesting to see the single values. Adequate interpretation of the course of insulin levels in normals is still difficult. It seems even more difficult in uraemics, as basal levels often change.

DRÜECKE One should not compare dialysis patients and undialysed patients together. The behaviour of the glucose curve after oral glucose load is not the same in dialysed patients as in undialysed patients. Probably the glucagon responsiveness is different before and after the patient has been started on dialysis. This might explain some of the difference.