Maintenance of Basal Plasma Glucose and Insulin Concentrations in Maturity-Onset Diabetes

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SUMMARY

Normal and mildly diabetic subjects each have their own "set" of basal plasma glucose and insulin concentrations. Diabetic patients have raised basal plasma glucose, with low-normal basal plasma C-peptide concentrations. Restoring normal glucose levels in mild diabetes by an insulin infusion further reduces the C-peptide concentration, but both the plasma glucose and the C-peptide return to their "set" level when the insulin is withdrawn. These results accord with the action of beta cells and liver in a negative feedback loop that maintains basal plasma glucose and insulin concentrations. DIABETES 28: 227–230, March 1979.

The overnight fasting plasma glucose concentration in maturity-onset diabetic patients persists at a raised level with little variation, and shows no tendency to fall toward normal levels in the absence of a nutrient load.[1,2] This raised basal plasma glucose concentration is a predominant metabolic abnormality, and in mildly diabetic patients it is more abnormal than the postprandial plasma glucose concentrations.[3] The fasting plasma insulin levels of mildly diabetic patients have been reported to be normal[4,5] or only slightly elevated,[6,7] and obese diabetic patients have raised plasma insulin levels comparable with those in similarly obese nondiabetic people.[8] This suggests that, in mildly diabetic patients, the basal insulin levels are maintained to a greater extent than the basal plasma glucose concentrations.

Nevertheless, in mildly diabetic patients, the basal plasma insulin concentration is dependent on the basal plasma glucose concentration, and is responsive to small plasma glucose variations.[9] If the plasma glucose level is reduced to normal values, then the peripheral basal plasma insulin concentration in these diabetic patients becomes subnormal.[10] We have, therefore, postulated that the raised basal plasma glucose concentration is required to stimulate near-normal portal basal plasma insulin levels from a reduced insulin secretory capacity.[11] We suggest that this arises because the liver and beta cells function in an integral feedback loop, which has a major role in controlling both the basal plasma glucose and the insulin concentrations. This paper reports three studies that are in accord with this hypothesis.

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METHODS

All three studies were performed in normal-weight (<15% over ideal weight)[12] mildly diabetic patients who had had no glycosuria or symptoms. They were treated only by diet, with energy intake restricted to maintain normal weight, but with normal nutrient proportions (50% of calories from carbohydrate, 35% from fat, and 15% from protein). All patients had been previously diagnosed by a raised fasting plasma glucose concentration (>6 mmol/L) together with either an abnormal oral or intravenous glucose tolerance test (plasma glucose 2 h after 50 g oral glucose > 8 mmol/L, or kg for 0.5 g/kg i.v. glucose < 1%/min, respectively). The patients were admitted overnight for the studies, and in the morning were kept rested in bed. Blood samples were taken via an indwelling Teflon catheter inserted into a forearm vein under local anaesthesia. The patients were asked to keep to their usual diet, and were not studied if they were unwell.

Repeatability of basal plasma glucose and insulin concentrations in normal and diabetic subjects. Nine diabetic and six normal subjects were admitted overnight on three occasions separated by 1–4 wk intervals. After their dinner at 1800 h they received no further food and blood samples were taken at 2-h intervals between 2300 and 0700 h, and then at 0800 h, with the patients recumbent.

Response to terminating insulin-induced normoglycaemia in mildly diabetic patients. Eight diabetic patients were each admitted for a control and an experimental night, allocated in random order. Blood samples were taken from

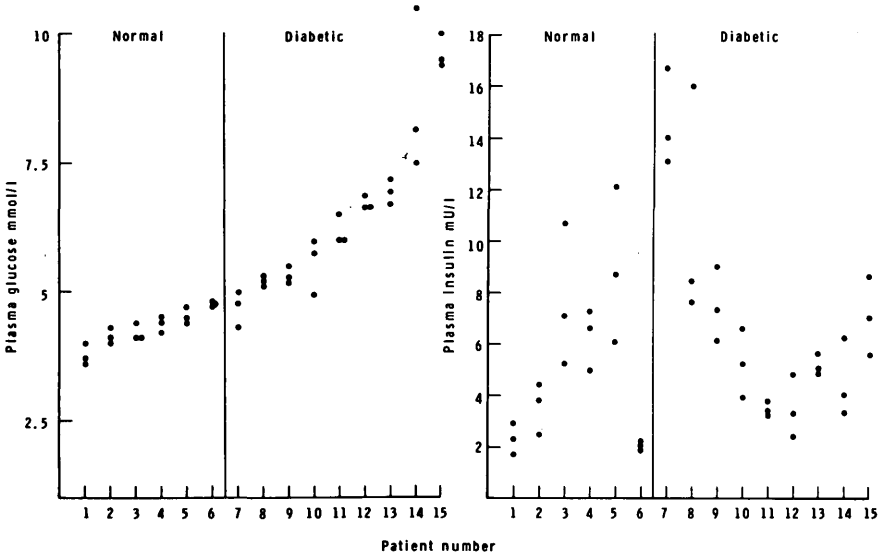

FIGURE 1. The 0700 h basal plasma glucose and insulin values of nine normal weight, maturity-onset diabetic and six normal subjects measured on three separate nights. The subjects are ranked in order of the height of their basal plasma glucose level.

1800 h, after which they had their normal evening meal, and overnight at intervals until 0900 h, during which time they were given no further food. On one evening an intravenous infusion of Actrapid insulin was administered between 1800 and 2200 h in order to reduce the plasma glucose concentration to normal (<5.5 mmol/L). Blood samples were then taken half-hourly until 0100 h, then 2-h until 0700 h, and hourly to 0900. The dose was estimated according to the height of their previously measured basal plasma glucose concentration,[10] and the rate of infusion altered according to the plasma glucose estimations taken at half-hourly intervals (Reflomat glucose oxidase sticks, Boehringer). On the control evening, saline only was infused for the same period.

Basal plasma insulin and C-peptide concentrations in diabetes. A basal blood sample was taken at 0700 h, with the patient rested overnight and fasted, in 27 diabetic and 15 normal subjects.

Plasma glucose estimations were done by the manual glucose oxidase method (Boehringer kit, GOD-perid) and plasma immunoreactive insulin was measured by using charcoal phase separation,[13] as was plasma immunoreactive C-peptide.[2] Plasma samples were stored at −20°C, and for studies 1 and 2 the samples were analyzed together in the same assay. Statistics include analysis of variance and Student's *t* test.

RESULTS

Overnight stability of basal plasma glucose and insulin concentrations in each individual. The glucose and insulin concentrations remained stable overnight. The mean plasma glucose concentrations in the normal and diabetic patients at 0100, 0300, 0500, 0700, and 0800 h were 4.3, 4.3, 4.3, 4.2, 4.1, and 6.2, 6.4, 6.6, 6.7, 6.7 mmol/L, respectively. The values for the plasma insulin were 5.1, 5.0, 5.1, 5.8, 6.0, and 7.7, 6.5, 6.9, 7.4, 7.9 mU/L, respectively. The mean of the variance, of the 0100, 0300, and 0500 h plasma glucose concentrations, on each of the three separate nights ranged 0.002–0.061 (mean 0.022) mmol/L in individual normal subjects, which is significantly ($P < 0.05$) smaller than in the diabetic patients, who ranged 0.013–0.260 (mean 0.102) mmol/L. The equivalent values for insulin 0.1–0.7 (mean 0.3) mU/L in normal subjects, which is not significantly different from those in the diabetic patients, which ranged 0.3–1.5 (mean 0.8) mU/L.

Day-to-day repeatability of basal plasma glucose and insulin concentrations. In each individual, the overnight plasma glucose concentrations were very similar on each of three different nights. The 0700 h fasting plasma glucose and insulin concentrations are shown in Figure 1. The day-to-day variance of the mean 0100, 0300, and 0500 h plasma glucose concentrations of normal subjects ranged 0.005–0.072 (mean 0.028) mmol/L in normal subjects, which is not significantly different from the values in diabetic patients, which ranged 0.005–0.43 (mean 0.163) mmol/L. The equivalent values for insulin ranged 0.01–3.2 (mean 0.99) mU/L in normal subjects, which is not significantly different from those in the diabetic patients, which ranged 0.01–8.6 (mean 2.1) mU/L. The repeatability of 0700 h is very similar, the mean coefficient of variation of the plasma glucose of normal and diabetic subjects being 4.0 and 6.2%, respectively, and for insulin 24 and 24%, respectively.

"Set" of basal plasma glucose and insulin concentrations in each individual. Each normal person has his own "set" of basal plasma glucose and insulin concentrations, in that the mean of the 0100, 0300, and 0500 h values in each of the six normal subjects on three different nights were closer than three readings on different individuals would have been by chance alone (variance ratios glucose $F = 8.4$, $P < 0.01$, insulin $F = 14.5$, $P < 0.001$). The difference between the "set" of the plasma glucose of each diabetic patient ($P < 0.001$) was greater than in the normal subjects, but normal and diabetics subjects had similar precision of the plasma insulin "sets" (Figure 1).

Return to basal plasma glucose and C-peptide values after termination of insulin-induced normoglycemia. Figure 2 shows the mean of the plasma glucose and C-peptide levels in the diabetic subjects during and after the insulin and saline infusions. The basal (0700 h) plasma glucose on the control night ranged 6–14 mmol/L (mean ± 1 SD, 9.4 ± 2.9 mmol/L). During the insulin infusion the plasma glucose concentration was reduced to between 2.9 and 5.3 mmol/L. The plasma glucose level after dis-

continuation of the insulin infusion rose in each patient ($P < 0.001$) up to the glucose concentration on the control night, the last statistically significant ($P < 0.01$) difference between the postinsulin and postsaline glucose concentrations being at 0500 h. At 0900 h, the mean difference between the plasma glucose concentrations in the 2 days was 0.9 (±1 SD, ±0.6) mmol/L, the correlation between the values being $r = 0.94$ ($P < 0.001$).

The plasma C-peptide concentrations were reduced pari passu with the glucose concentrations. The plasma C-peptide rose, after discontinuation of the insulin infusion, up to the level on the control night (23.30 h, 0.13 ± 0.08; 0900 h, 0.20 ± 0.12; mean ± SD, $P < 0.05$, Figure 2). The last statistically significant ($P < 0.02$) difference between the postinsulin and postsaline C-peptide concentrations was at 0100 h. The C-peptide concentrations of each patient at 0900 h on the 2 days were very similar (mean ± 1 SD, difference 0.07 ± 0.06 pmol/ml, correlation between values $r = 0.88$, $P < 0.001$).

Basal plasma insulin and C-peptide concentrations in diabetic patients. The diabetic patients all had a raised basal (0700 h) plasma glucose concentrations (Table 1). The mean basal plasma C-peptide concentration in the diabetic patients was significantly lower than in the normal subject ($P < 0.02$). The basal plasma insulin levels showed a similar trend, although there was not a significant difference.

FIGURE 2. Mean overnight plasma glucose and C-peptide concentrations of eight normal weight, maturity-onset diabetic patients. On one night, saline was infused (●) and on the other night (○) insulin was infused to lower the plasma glucose towards normal. Values significantly different from the 0900 h control baseline after saline infusion are indicated (*). Both glucose and C-peptide values rose after the insulin infusion was stopped at 2200 h.

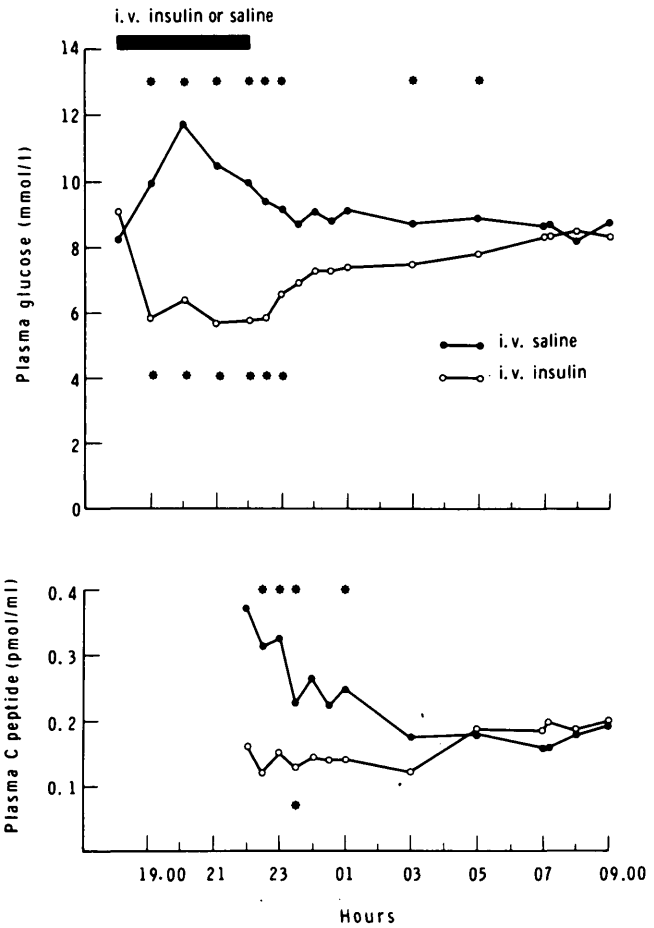

TABLE 1
Comparison of 0700 h basal plasma glucose, insulin, and C-peptide concentrations of normal and mildly diabetic subjects (mean ± 1 SD)

	Normal subjects	Mildly diabetic subjects	
Number	15	27	
Age	45 ± 6	52 ± 10	$P < 0.05$
Percent over ideal weight	7 ± 10	5 ± 5	NS
Basal plasma glucose (mmol/L)	4.3 ± 0.3	8.0 ± 2.9	$P < 0.001$
Basal plasma insulin (mU/L)	6.0 ± 3.1	5.1 ± 2.2	NS
Basal plasma C-peptide (pmol/ml)	0.30 ± 0.14	0.20 ± 0.12	$P < 0.02$

DISCUSSION

These studies show that both normal and diabetic subjects have a "set" of their basal plasma glucose and insulin concentrations. These concentrations are repeatable from night to night and characteristic for each person when healthy and in a given state of nutrition. If the raised basal plasma glucose concentrations of diabetic patients is lowered to normal, basal plasma insulin concentrations are reduced to subnormal levels.[9,10] The plasma C-peptide decrease, after reduction of the basal hyperglycemia by an insulin infusion in the second of the present studies, is in accord with the raised basal plasma glucose being required to maintain normal basal insulin secretion. In addition, when an insulin infusion is discontinued, both the plasma glucose and the C-peptide concentrations return to their original "set" levels. A lowered portal vein insulin concentration is probably the stimulus for this restoration, as it would allow a temporary increase in hepatic glucose efflux, and therefore a rise in the plasma glucose concentration. The accompanying return of the C-peptide concentration to its "set" level is in accord with the postulated feedback loop between the beta cells and the liver.[11] The low sensitivity of the periphery to small changes in insulin concentrations makes it less likely that peripheral glucose uptake modulation was involved.[14,15] One cannot exclude a role of neural regulation of plasma glucose and insulin concentrations, or for altered glucagon secretion, after the insulin infusion. However, an insulin infusion might be expected to decrease glucagon secretion, which might impair return of glucose concentrations to their previous "set." Recent studies suggest glucagon secretion might not have a major role in basal glucose homeostasis.[16,17]

The third study suggests the basal peripheral plasma insulin and C-peptide concentrations of normal-weight maturity-onset diabetic patients are in the lower part of the normal range, with the C-peptide levels significantly reduced. The less abnormal plasma insulin might be due to decreased hepatic clearance of insulin in diabetes, or to cross-reaction in the insulin immunoassay of the increased basal plasma proinsulin of maturity-onset diabetic patients.[18] A slight reduction in the portal vein plasma insulin

level may provide the "error signal" in the postulated feedback loop. Subnormal fasting plasma insulin or C-peptide levels have only rarely been reported in diabetic patients.[19] This may be because blood samples are usually taken when the patients are not completely rested, and the stress of coming fasting up to hospital raises the plasma glucose, insulin and C-peptide levels in diabetic but not in normal subjects.[20]

The steady-state plasma glucose and insulin levels achieved by a feedback loop would depend in part on the "sensitivity" of both the hepatic and the beta cell control elements. Thus a rise in the basal plasma glucose level could be induced by an increase in the degree of insulin "resistance" at the liver, as well as by decreased beta cell function. When there is insulin resistance, as in obesity, one would expect that the basal plasma insulin levels would be raised by the postulated feedback loop, until they are effective in inhibiting hepatic glucose efflux.[21] It has been reported that basal plasma insulin levels correlate with the degree of insulin resistance.[22] The similarity between the fasting plasma insulin levels of diabetic and nondiabetic obese subjects[8] is in accord with their plasma insulin concentrations being "set" in a feedback loop by the glucose concentration, with insulin resistance of the two groups being similar.

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