The Defective Glucose Sensitivity of the B Cell in Non Insulin Dependent Diabetes. Improvement After Twenty Hours of Normoglycaemia

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In non insulin dependent diabetics (N.I.D.D.) of normal body weight, the acute insulin response to glucose is defective while that to pharmacologic agents such as tolbutamide is less impaired. This specific B-cell insensitivity to glucose results from unknown and perhaps multiple mechanisms. Hyperglycemia may by itself aggravate this phenomenon. To test this hypothesis acute insulin release (ΔI: sum of increment at 2, 5, 10 min) after intravenous glucose and tolbutamide injection was studied in 5 N.I.D.D. with fasting blood glucose averaging 12.1 mM/l (range 10.7–13.7) before and after 20 hours of glycemic normalization by an artificial pancreas. Intravenous injection of .3 g/k glucose did not elicit an acute insulin or C-peptide response, but following Tolbutamide (20 mg/kg) ΔI was 44 ± 21 μU/ml and ΔC-peptide 0.84 ± 0.37 nM/l. After 20 hr of normoglycemia a response to glucose was apparent (ΔI 60 ± 24 and ΔCP 0.86 ± 26) that to Tolbutamide was unchanged (ΔI 58 ± 26 and ΔCP 0.97 ± 0.27). These results suggest that 20 hr of normoglycemia improve significantly the "glucoreceptor" function of the B-cell in N.I.D.D.

IN ADULTS with non insulin-dependent diabetes and normal body weight the acute insulin response to a glucose challenge is subnormal;[1,2,3,4] and the higher the fasting hyperglycemia, the lower the insulin response.[5,6,4] The diabetic B-cells appear to be insensitive specifically to glucose stimulation since other stimuli remain effective.[2,10,3,11]

Reducing basal hyperglycemia by appropriate treatment apparently partially restores the defective B-cell glucose-induced insulin response.[7,8,9] It has been postulated, therefore, that B-cell function can recover after a "resting" at normal blood glucose concentrations. In order to establish the role of basal hyperglycemia in possible B-cell "fatigue" with insensitivity to glucose, we have studied non insulin dependent diabetics of normal weight with a mean fasting hyperglycemia of 11 mmole/l, at which degree of hyperglycemia diabetics have no acute insulin response to intravenous glucose.[6,4] The insulin response to both intravenous glucose and tolbutamide was made before and after 20 hr of normoglycaemia obtained by insulin infusion through an artificial pancreas. Tolbutamide provokes insulin release in mild diabetes[2,11] as do secretine and isoproteronol. An increased response to both stimuli after normoglycaemia could be explained by an overall improved B-cell function following a period of "rest." On the other hand an isolated improved response to glucose would suggest recuperation of a specific gluco-receptor "insensitivity."

MATERIALS AND METHODS

Five non insulin-dependent adult diabetics of normal body weight, aged between 37 and 55 yr, and having diabetes for 10–30 yr, were studied (Table 1). They were on a 2,000 Kcal.diet with 225 g carbohydrates. Two patients (3 and 5) were on oral hypoglycemic agents which were stopped two days before the test. At this time plasma glucose levels ranged between 10 and 14 mmole/l and glycohaemoglobin between 7.9 and 9.1% (normal range 5.1 ± 1.2).[12]

An initial test of B-cell stimulation was done at 8 a.m. the first day using glucose and tolbutamide (see below). Then patients were put on the artificial pancreas (Biostator R) which permitted normalization of blood glucose values within 2 hours and maintained normal values until 8 a.m. the second day. Alimentation was continued during this time. Then, a second stimulation test identical to the first was performed.

These tests of stimulation which have been previously described and substantiated[11] were carried out in the following manner: two basal samples were taken at 15 min intervals, then 0.3 g/kg of a glucose solution injected intravenously over 2 minutes. Samples were taken at 2, 5, 10, 20, 30, 40, 50, 60, 90, and 120 min intervals following the injection. Then 20mg/Kg of Tolbutamide was injected over 2 minutes and samples taken 2, 5, 10, 20, and 30 min following. Plasma glucose levels were assayed by a Technicon autoanalyser, and insulin and C Peptide values determined by double antibody radioimmunoassay (C.E.A.-SORIN and Byk-Mallinckrodt kits respectively).

Results have been expressed as actual values and as the sum of increments above basal levels at 2, 5, and 10 min (Δ insulin, Δ C-peptide). The glucose disappearance rate (K value) after glucose infusion was calculated from the slope of the logarithm of the plasma glucose level from 5–50 min after intravenous glucose.

An identical stimulation test in 19 nondiabetic subjects of normal body weight and age between 20 and 40 yr, gave a Δ insulin value of 105 ± 6 μU/ml after glucose injection and 106 ± 8 after tolbutamide injection.[4]

Statistical analysis used the non parametric wilkoxon test for paired series.

RESULTS

For the initial stimulation test mean basal plasma glucose value was 12.6 m mole/l, plasma insulin 19.2 ± 8 μU/ml and plasma C-Peptide 0.50 ± 0.18 n mole/l. Glucose injection was not followed by early

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Table 1. Characteristics of the patients

	1	2	3	4	5
Sex	M	F	F	F	M
Age (yr)	55	37	45	55	53
Relative Body weight %	100	110	98	100	104
Diabetes duration (yr)	10	13	10	30	12
Family History of Diabetes	F-M	F	—	F-M	F
Fasting blood glucose m Mole/l	10.8	12.5	11.6	13.9	12.4
Glycohemoglobin %	8.4	8.1	7.9	9.1	8.6
Drug treatment	none	Metformine 1.700	Glibenclamide 5 mg	none	none

insulin secretion (Fig. 1). Tolbutamide injection, however, was followed by increased plasma insulin and C-Peptide levels.

Once patients were on the artificial pancreas, glycaemia returned to normal in 2 hr and remained so during the 20 hr session. During this time the mean dose of insulin infused was 46 U with range 30 to 70 U.

Before the second stimulation test began mean values were plasma glucose 5.7 m mole/l, plasma insulin 16.8 ± 2.9 μU/ml, and plasma C-Peptide

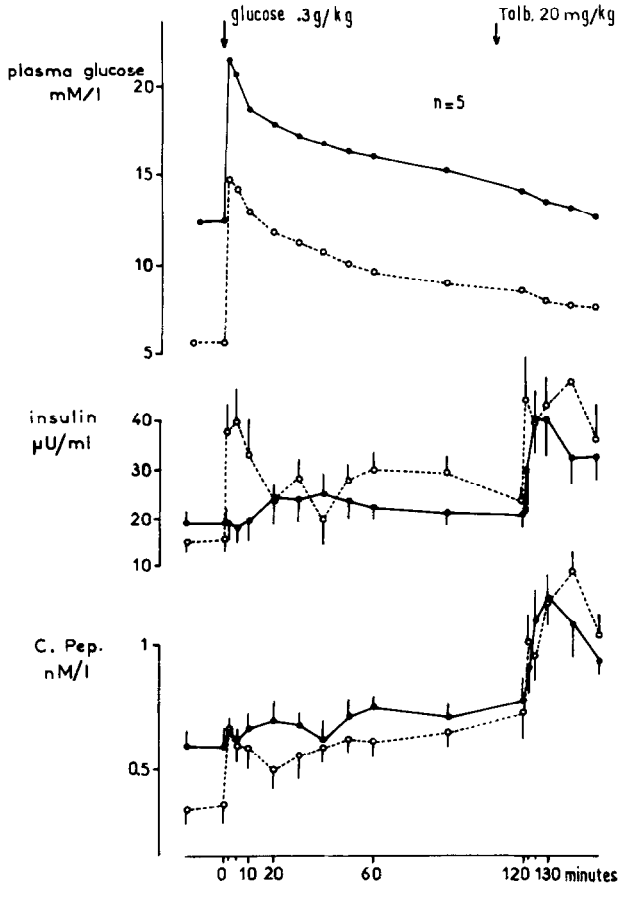

Fig. 1. Plasma glucose, insulin and C. Peptide values after stimulation by intravenous glucose then Tolbutamide in 5 N.I.D.D. Straight lines: untreated subjects. Dotted lines: after 20 hours of normoglycemia.

0.35 ± 0.12 nmole/l. These values were significantly lower than those observed before the first test for plasma glucose and C-Peptide ($p < 0.05$). Following glucose injection insulin and C-Peptide values rose immediately, while values obtained after tolbutamide injection were similar to those observed during the first stimulation test.

Table 2 shows Δinsulin and ΔC-Peptide values for each of the two tests. After glucose injection these values were near zero in the first test but rose significantly following the second stimulation. After, tolbutamide injection the insulin value which represented 40% of that found in nondiabetics of normal body weight, remained the same during both tests. Values were equally the same for C-Peptide. Mean K value was slightly higher on the second test ($0.38.10^{-2}$ versus $0.33.10^{-2}$) but not significantly.

DISCUSSION

This study confirms that the acute insulin response to glucose can be partially restored in non insulin dependent diabetics of normal body weight after a brief period of normal blood glucose level. In non insulin dependent diabetics with fasting blood glucose levels higher than 10 m mole/l, intravenous glucose does not provoke an acute insulin response.[6,4] The absence of such a response is partially due to reduced B-cell secretory capacity, but principally to specific insensitivity of these cells to glucose since other stimuli remain effective.[2,10,3,11] Following return to normal of fasting blood glucose levels basal insulin secretion falls as evidenced by decreased plasma insulin and, more importantly, C-Peptide whose longer half-life gives a more accurate reflection of basal secretion.

Holman and Turner[13] suggested the basal insulin secretion is adjusted by the blood glucose level via a control loop involving B-cells, portal blood insulin level, its effect on hepatic efflux of glucose, the resulting blood glucose concentration and in turn B-cell stimulation by arterial glucose. Thus in the diabetic subject an elevated basal blood glucose level is needed to induce a near-normal basal plasma insulin concentration since B-cell function is diminished. In accord

Table 2. The Effect of Normalization of Plasma Glucose on Plasma Insulin, C. Peptide and Glucose Disappearance Rate (K values) in NIDDM Tested With Acute Glucose or Tolbutamide Injection

	Plasma insulin uU/ml				C. Pep. nMole/l				K values × 10^2	
	1st test		2nd test		1st test		2nd test		1st test	2nd test
Subjects	ΔG	ΔT	ΔG	ΔT	ΔG	ΔT	ΔG	ΔT		
1	−5	2	33	0	.39	.42	1.06	.27	.35	.27
2	1	120	121	152	.24	1.17	1.81	1.66	.39	.44
3	−21	41	28	50	−.12	.87	.87	.68	.42	.49
4	−2	52	7	76	.12	2.01	.14	1.52	.16	.33
5	21	4	111	16	.30	−.21	.42	.71	.32	.40
$\bar{m}$	−1.2	44	60	58	.18	.84	.86	.97	.33	.38
s.e.m.	6.7	21.4	23	26	.09	.37	.29	.27		
		p. < 0.05				p. < 0.05				

with that, we found reduction of the blood glucose concentrations to normal resulted in decreased basal insulin secretion. On the other hand restoring blood glucose levels to normal reestablished an acute insulin response to intravenous glucose. Similarly in juvenile type of diabetes, during the remission period, reduction of fasting hyperglycemia following treatment results in a improved insulin response after oral glucose administration.[14] In non-insulin dependent diabetics, this is found regardless of treatment by exogenous insulin, in which B-cells would remain unstimulated,[8] by sulfonylureas[7] or by diet alone.[9] Therefore, it seems likely that it is not the treatment itself that is responsible for improved pancreatic B-cell function, but rather corrected metabolic abnormalities and especially hyperglycemia.[15]

It may be observed that the partial restoration of early insulin response to intravenous glucose after plasma glucose normalization was not escorted by a significant improvement of glucose disappearance rate. Similar findings were reported by Hecht et al.[7] after treatment of non insulin dependent diabetics for eight days by chlorpropamide and by Turner et al.[8] after a day long insulin infusion. This fact may be indicative of insulin resistance or possibly of down regulation of insulin receptors by the required insulin infusion over the 20 hr prior to the second test.

The insulin response to tolbutamide given following the intravenous glucose load remained unchanged after normalization of the fasting hyperglycaemia. Similarly Halter et al.[16] have reported that as the insulin response to glucose is increased by reduction of the blood sugar, the isoprenalin response is decreased. Thus, the changes seen in insulin secretion do not appear to be a restored B-cell capacity of insulin synthesis, nor a reappearance of an acutely releasable pool which would be absent in permanently over stimulated cells. Therefore the result suggests an amelioration of the B-cell "gluco-receptor" function. To explain this phenomenon several hypotheses are possible. Chronic hyperglycemia may decrease B-cell sensitivity of the gluco-receptor system by a mechanism of down regulation such as that observed in interactions between protein hormones and their receptors. On the other hand Karam et al.[17] have shown in normal subjects and in obese non diabetic patients that while a sudden elevation of blood glucose levels causes an insulin spike, this response is greatly diminished or even suppressed when blood glucose levels are artificially elevated to values exceeding 11 m mole/l. These observations complement those obtained in the present study. When basal hyperglycemia exists B-cells are no longer capable of responding to acute glucose infusion whether the patients are diabetic or not.

It is possible that glucose receptor sites are occupied and therefore unable to respond to a new stimulation regardless of their membrane or intra cellular localisation and of their nature as metabolites or signals.

In any case a primary defect in the glucose sensitivity of the B-cells seems to exist in non insulin dependent diabetes as exemplified by the low insulin responses to glucose of offsprings of diabetic parents.[18,19,20] This primary defect may be amplified in the permanent hyperglycemia state. However we observed that 2 of 5 diabetics did recover a normal insulin release to glucose stimulation. This fact leaves open the possibility the syndrome of non insulin dependent diabetes is made up by various types of B-cells anomalies.

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