The Magnitude, the Kinetics and the Metabolic Efficiency of First-Phase Insulin Response to Intravenous Glucose are Related

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Summary

We investigated the relationship between the kinetics, the magnitude and the metabolic efficiency of first-phase insulin response (FPIR) to intravenous glucose. Twenty healthy control subjects and fifty first degree relatives of Type 1 diabetic patients were studied using a standardized protocol for the intravenous glucose tolerance test (IVGTT). The first significant increase in plasma insulin concentrations above baseline appeared as early as the 2nd min (1 min before the end of glucose injection, fast response) in 80 % of controls and 70 % of relatives, and at the 3rd min or later (delayed response) in the remaining subjects. The greatest delay in insulin release (5th min) was observed in 4 of 6 relatives of Type 1 diabetic patients with impaired FPIR. In the controls and the relatives, the subjects with a fast insulin response had a significantly higher FPIR (controls 215.4±93.5 vs 59.7±5.6 μU/ml, $p<0.001$ and relatives 143.5±61.8 vs 55.9±27.7 μU/ml, $p<0.001$) and showed better glucose assimilation (controls 3.05±1.05 vs 1.64±0.16 %/min, $p<0.05$ and relatives 2.6±0.96 vs 1.6±0.85 %/min, $p<0.01$) during IVGTT than the subjects with a delayed response. Moreover, for normal FPIR values in the group of relatives of Type 1 diabetic patients, a fast response was associated with a significantly better glucose assimilation as assessed by the incremental area under the glucose curve (358.6±64.7 vs 539.2±67.7 mmol/l per 90 min, $p<0.001$). These data show 1) that minor variations in the speed of early insulin release (i.e., 1 min) might have important effects on glucose tolerance during IVGTT in healthy subjects and 2) that an impaired FPIR to intravenous glucose is clearly associated to a delayed insulin release.

Key words

Insulin Secretion – First Phase Insulin Response – IVGTT – Pre-Type 1 diabetes

Introduction

Physiological insulin response to intravenous glucose bolus is characterized by an early peak of insulin release within the first 10 min (first-phase) followed by a progressive decline of insulin concentrations reaching basal state within 60 to 90 min. Loss of the first-phase insulin response (FPIR) to intravenous glucose is a common characteristic of the early stage of both insulin-dependent (Type 1) and non-insulin-dependent (Type 2) diabetes mellitus (*Ganda, Srikanta, Brink, Morris, Gleason, Soeldner* and *Eisenbarth* 1984; *Ward, Bolgiano, McNight, Halter* and *Porte* 1984). Moreover, a progressive decline of FPIR can be detected several years before the onset of Type 1 diabetes (*Srikanta, Ganda, Gleason, Jackson, Soeldner* and *Eisenbarth* 1984). The intravenous glucose tolerance test (IVGTT) is now used along with the immunological markers for identifying individuals at high risk of diabetes in populations such as first degree relatives of Type 1 diabetic patients (*Vardi, Crisa, Jackson, Dumont Herskowitz, Wolfsdorf, Einhorn, Linarelli, Dolinar, Wentworth, Brink, Starkman, Soeldner* and *Eisenbarth* 1991). In association with this quantitative defect in peak insulin, it has been shown that the first-phase insulin response to intravenous glucose load was delayed in mild diabetic patients compared with normal individuals (*Thorell, Nosslin* and *Sterky* 1973; *Reaven, Shen, Silvers* and *Farquhar* 1977; *Seltzer, Allen, Herron* and *Brennan* 1967). However, in addition to a wide interindividual physiological variation in insulin response after intravenous glucose, IVGTT has only been standardized recently, leading to difficulties in interpreting data from different study groups, since the first-phase insulin response is highly dependent on the dose of glucose and the duration of intravenous injection (*Fujita, Herron* and *Seltzer* 1975). We studied the kinetics of the first-phase insulin response to intravenous glucose and its relationship to quantitative insulin secretion and glucose assimilation in non obese healthy controls and first degree relatives of Type 1 diabetic patients, with special attention to insulin and glucose measurements during and immediately after glucose injection, using a standardized protocol for the intravenous glucose tolerance test.

Sujects, Materials and Methods

Subjects

Twenty healthy volunteers without family history of diabetes mellitus were studied as a control population. Fifty first degree relatives of Type 1 diabetic patients included in a screening program for prevention of Type 1 diabetes were examined consecutively. There were 3 parents (2 mothers and 1 father), 10 siblings (6 sisters and 4 brothers) and 35 offspring (18 daughters and 17 sons) of 21 Type 1 diabetic patients. Subjects under the age of 4 years and overweight individuals (body mass index (BMI) > 27 kg/m^2) were not included in the study.

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There was no significant difference between controls and relatives of diabetic patients in age (27 ± 2.7 vs 21.5 ± 13.4 years respectively), sex (7 women, 13 men vs 26 women, 24 men respectively) or BMI (22 ± 3 vs 20.7 ± 3.5 kg/m^2 respectively). Informed consent was obtained from all subjects or their parents after the nature of the study was fully explained.

Intravenous glucose tolerance test

Subjects were studied between 0800 and 0900 hours after an overnight fast and were asked to be on an unrestricted diet and to exert normal physical activity for three days before the test. The design of the IVGTT was drawn up according to a standardized protocol recently proposed (*American Diabetes Association* 1990), except for the use of a 30% (instead of 25%) glucose solution for intravenous injection. Glucose at 0.5 g per kg body weight (max. 100 ml = 30 g) was injected manually into a forearm vein over 180 ± 15 s and the injection was timed to ensure a steady infusion rate. Venous blood was sampled from an opposite forearm vein by means of a blood sampler automate (IRTN, Toulouse, France). Sampling times were chosen in an attempt to determine the start of the insulin and glucose responses as precisely as possible. Two baseline samples were taken at – 15 and 0 min (beginning of the glucose injection) and then at 1, 2, 3 (end of injection), 4, 5, 6, 7, 8, 9, 13, 23, 33, 60 and 90 min. Plasma glucose was assayed on the same day of the test using the glucose oxidase method with a Beckman Glucose Analyser 2. Aliquots for plasma insulin measurement were stored frozen until determination of immunoreactive insulin (IRI) plasma levels by a standardized and quality-controlled double antibody radioimmunoassay (SB-INSI-5, CIS Biointernational, France) with 6.5% intra-assay coefficient of variation at 25 μU/ml, and 9.5% at 80 μU/ml. Fasting plasma IRI and glucose levels were means of values from the two baseline samples. Glucose and insulin responses were expressed as incremental areas above fasting concentration from 0 to 13 min (G 0–13 min area, I 0–13 min area) or from 0 to 90 min (G 0–90 min area, I 0–90 min area). The rate of glucose disappearance (Kg) was calculated between 13 and 33 min by least squares fitting from the curve of log glucose concentrations versus time (*Conard* 1955). Insulin response was also expressed as the sum of the insulin values at 1 and 3 min after the end of glucose injection (I1 + 3), corresponding respectively to the 4th and 6th min in this protocol, zero time being defined as the start of glucose injection. We considered the start of insulin response as the time of appearance of the first IRI value higher than basal IRI + (3 · [basal IRI · intra-assay CV %]).

Detection of islet cell antibodies (ICA)

Sera were tested for IgG-ICA by indirect immunofluorescence on cryostat sections of blood group 0 human pancreas. ICA positive and negative control sera were included in each assay. Subjects were considered as ICA positive if two consecutive samples were found positive.

Statistical analysis

Simple regression analysis was used to evaluate correlations between FPIR and Kg. Differences between groups were analysed by Student's t-test.

Results

Insulin and Glucose Responses

Data from insulin and glucose responses in the two groups studied are shown in Table **1**. We found a relatively high variability (coefficient of variation = SD/mean × 100 [%]) for insulin secretion in controls (n = 20, I 1 + 3 = 56%, I 0–13 min area = 56% and I 0–90 min area = 47%) as well as in relatives (n = 50, I 1 + 3 = 56%, I 0–13 min = 66% and I 0–90 min = 67.5%). Similarly, the coefficients of variation of total glucose response and Kg were relatively variable (controls 24% and 40% respectively, relatives 32% and 44% respectively), while the early glucose burst was remarkably constant between subjects (controls 17.5% and relatives 15%). Significantly lower FPIR was observed in the group of first degree relatives of Type 1 diabetic patients than in the control group ($p < 0.01$). Six (12%) of the 50 first degree relatives of Type 1 diabetic patient had an abnormal (low) acute insulin response. Due to the small number of control subjects, a low acute insulin response was defined arbitrarily as I 1 + 3 ≤ 40 μU/ml, according to the results from several study groups using the same IVGTT protocol (*Vardi* et al. 1991; *Chase, Voss, Butler-Simon, Hoops, O'Brien* and *Dobersen* 1987). FPIR and Kg were positively correlated in the group of relatives of diabetic patients ($r = 0.56$, $p < 0.01$) (Fig. **1**), but not in the control group ($r = 0.24$, $p > 0.05$).

Table 1 Insulin and glucose responses during IVGTT in control subjects and relatives of type 1 diabetic patients.

	Control Subjects (n = 20)	Relatives of type 1 diabetic patients (n = 50)
Fasting plasma glucose (mmol/l)	4.72 ± 0.43	4.86 ± 0.45
Glucose 0–13 min area (mmol/l per 13 min)	147.6 ± 25.8	141.4 ± 21.5
Glucose 0–90 min area (mmol/l per 90 min)	394.2 ± 95.8	422.6 ± 113.2
Kg (%/min)	2.84 ± 1.16	2.32 ± 1.02
Fasting plasma insulin (μU/ml)	8.06 ± 2.7	8.96 ± 3.16
I 1 + 3 (μU/ml)	186.2 ± 104	118.2 ± 71.7[a]
Insulin 0–13 min area (μU/ml per 13 min)	737.2 ± 406.9	469.8 ± 309.4[a]
Insulin 0–90 min area (μU/ml per 90 min)	2046 ± 955	1704 ± 1146

All data are expressed as mean ± SD.
[a] $p < 0.01$ versus control group

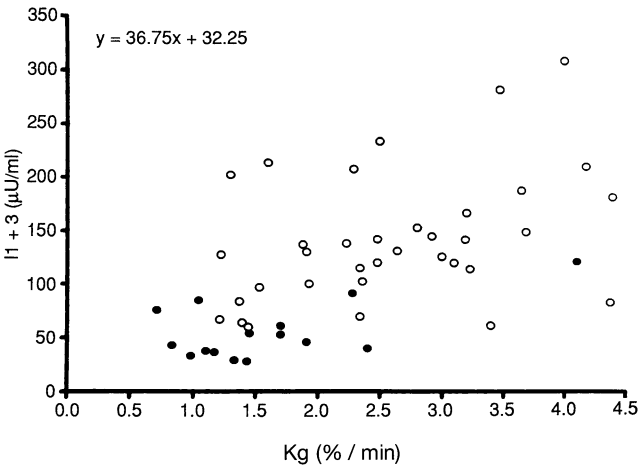

Fig. 1 Relationship between glucose assimilation (Kg) and first-phase insulin response (I 1 + 3) during IVGTT in first degree relatives of Type 1 diabetic patients (n = 50, r = 0.56, $p < 0.01$) (○ = fast response group, n = 35 and ● = delayed response group, n = 15).

Table 2 Comparison of insulin and glucose responses during IVGTT between fast and delayed response groups in control subjects and relatives of Type 1 diabetic patients.

	Control subjects		Relatives of Type 1 diabetic patients	
	Fast response (n = 16)	Delayed response (n = 4)	Fast response (n = 35)	Delayed response (n = 15)
Fasting plasma glucose (mmol/l)	4.75 ± 0.33	4.53 ± 0.33	4.82 ± 0.44	5 ± 0.56
Glucose 0–13 min area (mmol/l per 13 min)	150.3 ± 26.5	137 ± 19.7	140.4 ± 20.6	144.5 ± 24
Glucose 0–90 min area (mmol/l per 90 min)	362.6 ± 83	510 ± 22[c]	381.6 ± 96.1	533.1 ± 72.6[c]
Kg (%/min)	3.05 ± 1.05	1.64 ± 0.16[a]	2.6 ± 0.96	1.6 ± 0.85[b]
Fasting plasma insulin (μU/ml)	8.31 ± 2.89	6.67 ± 1.7	9.56 ± 3.2	7.33 ± 2.5[a]
I 1 + 3 (μU/ml)	215.4 ± 93.5	59.7 ± 5.6[c]	143.5 ± 61.8	55.9 ± 27.7[c]
Insulin 0–13 min area (μU/ml per 13 min)	874.5 ± 394.3	269 ± 61.8[c]	585.7 ± 291.6	190.4 ± 89.1[c]
Insulin 0–90 min area (μU/ml per 90 min)	2299 ± 1002	1301 ± 369[a]	2035 ± 1179	878 ± 450[c]
0–13 min insulin/glucose ratio	5.8 ± 3.37	2.04 ± 0.71[c]	4.59 ± 1.77	1.09 ± 0.47[c]
0–90 min insulin/glucose ratio	6.8 ± 2.93	2.58 ± 0.82[c]	5.98 ± 2.69	1.76 ± 0.93[c]

All data are expressed as mean ± SD.
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ versus fast response group in each population

Kinetics of First-Phase Insulin Release

The first significant increase in plasma IRI values above baseline was observed at the 2nd min (1 min before the end of glucose injection) in 16 (80%) of the 20 control subjects, and at the 3rd min (end of injection) in the remaining 4 controls. In the group of relatives of Type 1 diabetic patients, the start of insulin response was at time 2 min for 35 (70%), at 3 min for 11 (22%) and at 5 min for 4 subjects (8%). Within each of the two populations studied, we compared individuals with an insulin response starting at 2 min (fast response groups, 16 controls and 35 relatives) with those with a response starting at 3 min or later (delayed response groups, 4 controls and 15 relatives). As shown in Table **2** and Figures **1** and **2**, a delayed insulin response was associated with a significantly reduced insulin output ($p < 0.001$), glucose assimilation ($p < 0.01$) and insulin/glucose ratio ($p < 0.001$) compared with the fast response, in the control subjects and relatives of Type 1 diabetic patients. The rate of plasma glucose increase (Fig. **2**) and the early glucose response (G 0–13 min area) was quite identical for controls and relatives with a fast or delayed response. The start of insulin response was particularly delayed in the 6 relatives with impaired FPIR (I 1 + 3 < 40 μU/ml). Indeed, 4 of them began at 5 min and the 2 others at 3 min. Data from these six individuals are presented in Table **3**.

In order to estimate the effect of the delay in the insulin response on glucose assimilation during IVGTT, we compared 8 relatives with a fast response to 7 with a delayed response, all with an FPIR (I 1 + 3) ranging from 50 to 100 μU/ml (Table **4**). These two groups were matched on the basis of age and body mass index. First-phase and total insulin responses were not different between these two groups. However, individuals with a delayed response had a significantly higher incremental glucose response (G 0–90 min area 358.6 ± 64.7 vs 539.2 ± 67.7 mmol/l per 90 min, $p < 0.001$) and a lower 0–90 min insulin/glucose ratio (3.176 ± 1.92 vs 2.17 ± 1.03, $p < 0.05$), compared with the fast response group. Glucose assimilation was also lower in this group, but the difference was not significant. Two of the 50 relatives of type 1 diabetic patient were islet-cell antibody positive, one in the fast response group and the other in the delayed response group.

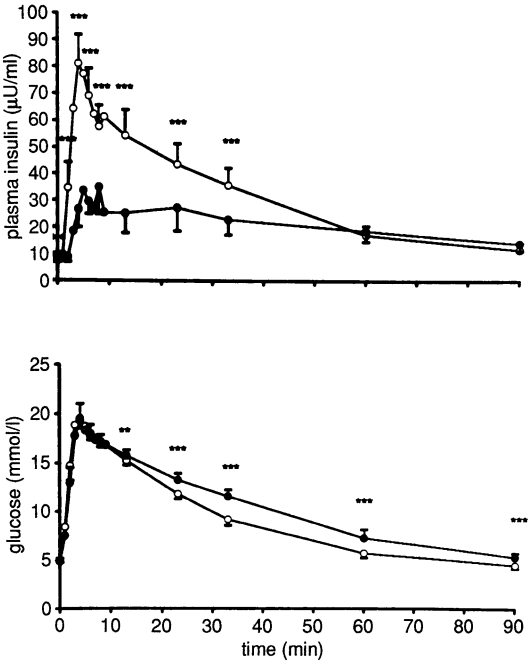

Fig. 2 Plasma insulin and glucose responses (mean ± SEM) during IVGTT in first degree relatives of Type 1 diabetic patients with fast (–○–, n = 35) or delayed (–●–, n = 15) early insulin release. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Discussion

Our results show evidence for a clear-cut variability in the rate of insulin response, positively correlated with insulin release and glucose tolerance during IVGTT, in healthy individuals with or without family history of type 1 diabetes mellitus. A progressive decrease in first-phase insulin response to intravenous glucose is a characteristic finding in the early stage of both Type 1 and Type 2 diabetes mellitus (*Ward* et al. 1984; *Srikanta* et al. 1984). This quantitative defect has been demonstrated to be associated with a slower (or delayed) insulin response in mild diabetic individuals (*Thorell, Nosslin* and

Table 3 Data from six subjects with low first-phase insulin response to intravenous glucose (I 1 + 3 < 40 μU/ml).

Subjects	Start of insulin response (min)	Age (years)	BMI (Kg/m^2)	Sex	Glucose				Insulin			
					Basal (mmol/l)	Kg (%/min)	0–13 min area mmol/l/ 13 min)	0–90 min area (mmol/l/ 90 min)	Basal (μU/ml)	I 1 + 3 (μU/ml)	0–13 min area (μU/ml / 13 min)	0–90 min area (μU/ml / 90 min)
1	fifth	17	22.4	M	4.5	0.98	108	566	8	33	73	1001
2	third	22	17.9	W	3.9	1.17	163	551	7	37	139	527
3	fifth	51	18.3	W	5.4	1.43	133	548	7	28	142	452
4	third	28	21.6	M	5	1.33	150	541	5	29	119	251
5	fifth	10	16	W	4.8	2.4	125	375	3	40	142	406
6	fifth	27	21	M	5.7	1.1	128	473	5	38	128	702
mean		25.83	19.53		4.88	1.40	134.50	509.00	5.83	34.17	123.83	573.17
SD		14.02	2.50		0.64	0.51	19.44	73.23	1.83	4.96	26.51	262.16

Table 4 Plasma insulin and glucose response in relatives of Type 1 diabetic patients with fast and delayed early insulin responses.

	Fast response (n = 8)	Delayed response (n = 7)
Age (years)	19.25 ± 15.2	20.5 ± 14.3
Body mass index (Kg/m^2)	20.1 ± 3.1	20.7 ± 4.5
I 1 + 3 (μU/ml)	73.5 ± 13.3	70.2 ± 16.6
Kg (%/min)	2.13 ± 1.17	1.48 ± 0.55
Glucose 0–90 min area (mmol/l per 90 min)	358.6 ± 64.7	593.2 ± 67.7[b]
Insulin 0–90 min area (μU/ml per 90 min)	1359 ±736	1156 ±506
0–90 min insulin/glucose ratio	3.76 ± 1.92	2.17 ± 1.03[a]

Subjects are matched on the basis of age, body mass index and FPIR values. All data are expressed as mean ± SD.
[a] $p < 0.05$, [b] $p < 0.001$

Sterky 1973; *Reaven* et al. 1977; *Seltzer* et al. 1967). However, the choice of a particular IVGTT protocol (i.e., dose of intravenous glucose and speed of injection) seems to be of critical importance in analyzing the insulin response to intravenous glucose. Indeed, *Fujita, Herron* and *Seltzer* (1975) previously showed that a two-minute intravenous glucose injection induced faster and higher insulin output than did a five-minute injection, in both normal and mild diabetic subjects. *Rayman, Clark, Schneider* and *Hales* (1990), using a two-minute glucose injection (0.3 g/kg), failed to detect any variability in the kinetics of insulin release in 10 normal subjects, all exhibiting a significant increase in IRI concentrations at the 2nd minute. In this study, the fast but not maximal rise in blood glucose obtained with a three-minute glucose injection seems to unmask some slight variability in the rate of the insulin response in normal control subjects and in healthy first degree relatives of Type 1 diabetic patients. Blood glucose values within the first 4 min of IVGTT (Fig. **2**), as well as the acute glucose response (G 0–13 min area) (Table **2**) did not differ between the fast and the delayed response groups. Thereby, the variability observed in the swiftness of insulin release is unlikely to be explained by a difference in the rate of blood glucose increase during glucose injection.

The difference observed for insulin secretion between controls and relatives results, at least in part, from the presence of 6 (12%) low responding first degree relatives. However, the mean I 1 + 3 value remains significantly lower in relatives after removal of these 6 individuals (132 ± 68 vs 186.2 ± 104 μU/ml, $p < 0.05$), but this low value might also be accounted for by the difference in age distribution between the two populations studied. The impaired first-phase insulin response observed in pre-Type 1 diabetes is generally ascribed to the loss of pancreatic β-cell mass due to a selective autoimmune destruction. However, the hypothesis of a specific functional alteration of insulin secretion in response to glucose stimulus is supported by several studies showing that the insulin response to arginine or glucagon persists in pre-Type 1 diabetes, while the insulin response to glucose has disappeared (*Bardet, Pasqual, Maugendre, Remy, Charbonnel* and *Sai* 1989; *Bardet, Rohmer, Maugendre, Marre, Semana, Limal, Allanic, Charbonnel* and *Sai* 1991). Our results clearly show that the early insulin response to intravenous glucose is markedly delayed in relatives of Type 1 diabetic patients with impaired first-phase insulin response. Furthermore, the amplitude of the first-phase insulin response was significantly lower in control subjects or first-degree relatives of diabetic patients presenting a slight delay in the acute insulin response (3rd min), compared to those having a fast response (2nd min). The relationship between the kinetics and the magnitude of the insulin response found in healthy control subjects and in relatives of Type 1 diabetic patient suggests that some discrete functional abnormality might be involved in the weakness of the first-phase insulin response to intravenous glucose. However, as much as 4 out of 20 (20%) controls and 9 out of the 44 relatives (20%) with normal FPIR had a delayed insulin response. Since no more than 0.5% of normal controls and about 5% of first degree relatives will develop diabetes later on, it is unlikely that a delayed insulin response to intravenous glucose should directly contribute to the development of Type 1 diabetes mellitus.

The physiological importance of the early phase of insulin secretion in response to intravenous glucose is now well documented. Pharmacologically induced loss of early insulin release has been shown to be responsible for decreased glucose tolerance after intravenous glucose bolus (*Calles-Escandon* and *Robbins* 1987) mostly due to a marked delay in the inhibition of hepatic glucose production (*Luzi* and *De Fronzo* 1989). In this study, we confirm that first-phase insulin secre-

tion is correlated with glucose tolerance during IVGTT, in a population of healthy relatives of Type 1 diabetics. Furthermore, for comparable values of first-phase insulin response, individuals with fast insulin response (2nd min) showed better glucose assimilation than individuals with a delayed response (3rd min). This suggests that in addition to the amount of insulin released, the kinetics of the FPIR could have important physiological effects on glucose assimilation.

Using a well-standardized protocol for IVGTT, we provide evidence for slight physiological variations in the kinetics of the first-phase insulin response to an intravenous glucose load in healthy subjects with or without family history of Type 1 diabetes mellitus. A delay of only one minute in the start of the acute insulin response was associated with a lower insulin output and glucose assimilation, and for a comparable peak insulin value, a delayed response led to a lower glucose tolerance. Furthermore, the rate of response was markedly delayed in first degree relatives of Type 1 diabetic patients with impaired FPIR. The mechanisms unerlying the relationship between the kinetics and the amplitude of FPIR are at present unknown. However, both of these parameters could have an important physiological effect on glucose tolerance.

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