ORIGINALS

The Occurrence of Low Insulin Response to Glucose Infusion in Children

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Summary. Insulin response to glucose infusion was studied in 42 children with a normal intravenous glucose tolerance, 7–16 years of age. The majority of these children had at least one first degree relative with diabetes mellitus. Low and delayed insulin response similar to the one found in 15–20% of healthy adult subjects also occurred in 15–20 per cent of the children in this material. These findings support our previous suggestion that the low and delayed insulin response to glucose is probably genetically determined.

L'existence de réponse insulínique réduite à la perfusion de glucose chez l'enfant

Résumé. La réponse insulínique à la perfusion de glucose a été étudiée chez 42 enfants âgés de 7 à 16 ans et ayant un test de tolérance au glucose normal. Chez la plupart des enfants au moins un des parents ou frères et sœurs avait le diabète. Une réponse insulínique réduite et retardée, similaire à celle observée chez 15 à 20% des adultes en bonne santé, a été démontrée chez 7 enfants

sur les 42. Ces résultats confirment notre suggestion que ce type de réponse insulínique réduite et retardée est probablement déterminée par des facteurs héréditaires.

Das Vorkommen von verringerter Insulinausschüttung nach Glukoseinfusion bei Kindern

Zusammenfassung. Die Insulinausschüttung nach Glukoseinfusion wurde bei 42 Kindern, 7–16 Jahre alt, mit normaler intravenösen Glukosetoleranz untersucht. Die Mehrzahl dieser Kinder hatte einen diabeteskranken Eltern- oder Geschwisterteil. Eine verzögerte und verringerte Insulinfreisetzung, ähnlich denen, die bei 15–20% von gesunden Erwachsenen gefunden worden waren, war bei 7 von 42 Kindern zu sehen. Dieser Befund stützt unsere frühere Ansicht, daß die verzögerte und verringerte Insulinausschüttung bei Hyperglykämie wahrscheinlich genetisch bedingt ist.

Key-words: Children, insulin response, glucose infusion, prediabetes.

Introduction

On the basis of the findings in our previous studies we characterized prediabetes as a state where the insulin response to glucose infusion is of the type seen in overt and latent diabetes, *i. e.* sluggish and delayed, in spite of a normal glucose tolerance (Cerasi and Luft, 1963, 1967a, b, c). Since the type of insulin response was identical within monozygotic twin pairs we suggested that this response was genetically determined (Cerasi and Luft, 1967b).

Our previous studies were performed on adult subjects. It was considered of importance to find out whether the sluggish and delayed insulin response was also present in children. For this purpose the insulin response to glucose infusion was studied in 42 healthy children, most of whom had a family history of diabetes.

Subjects and Methods

The material comprised 42 children, 19 boys and 23 girls, aged 7–16 years (Table 1). In 29 of the children either one or both parents or one sibling had diabetes. Subjects nos. 5 and 16 were monozygotic twin brothers to diabetics.

Blood glucose was determined with a commercial glucose oxidase reagent (Kabi Reagent, Sweden). Glucose tolerance tests were performed, and the dis-

appearance rate of glucose (k -value) calculated, according to Ikkos and Luft (1957). Plasma insulin was determined by the radioimmunological procedure of Hales and Randle (1963).

The glucose infusion test (GIT) was performed as described previously (Cerasi and Luft, 1967a). The priming dose of glucose was 500 mg per kg body weight, the infusion rate of glucose 20 mg per kg per minute.

The relationship between blood glucose and plasma insulin concentrations during GIT was calculated by analogue computation of the glucose and insulin curves. This relationship is characterized by the following parameters:

- k_{11} a constant determining the amount of insulin released initially in proportion to the rise of blood glucose
- k_{12} a constant determining the amount of insulin produced and released postinitially during GIT in relation to the glucose level
- b expressing the slope of plasma insulin increase due to glucose infusion
- k_g a constant determining the effect of plasma insulin on glucose uptake

For a detailed description of the mathematical basis of these parameters, see Cerasi (1967). Fig. 1 illustrates schematically the parts of the glucose and insulin curves influenced by the above parameters. These curves also represent an average of those ob-

Table 1. Data on patient material and results of glucose infusion tests

No.	Initials	Sex	Age y	k -value	family history of diabetes	remarks	Computer parameters			
							k_{11}	k_{12}	b	k_g
1	I.A.	F	7	2.0	mother etc.	dizygote	2.396	2.669	2.272	1.476
2	O.A.	M	11	1.3	"	"	2.277	2.811	2.316	1.438
3	Y.A.	F	7	1.6	"	dizygote	2.449	2.707	2.246	1.609
4	E.A.	F	13	1.6	0	"	1.799	2.885	2.182	1.292
5	E.B.	M	7	1.2	twin brother	monozyg.	1.799	2.470	1.708	1.609
6	T.F.	F	11	2.3	father etc.	"	1.703	2.526	1.681	1.521
7	E.F.	F	8	2.3	mother etc.	"	2.079	2.290	1.191	1.840
8	I.M.F.	F	10	2.1	"	"	2.286	2.420	2.072	1.538
9	J.F.	M	9	2.3	father	"	2.386	2.459	2.093	1.520
10	L.F.	M	11	1.7	"	"	2.923	3.029	2.949	0.898
11	S.F.	M	13	1.9	"	"	2.004	2.474	2.013	1.459
12	M.H.	M	10	2.8	mother	"	2.173	2.501	1.892	1.851
13	S.H.	M	8	2.2	"	"	2.076	2.310	1.940	1.831
14	H.I.	M	9	1.8	father	"	1.398	2.371	1.763	1.635
15	A.C.K.	M	7	2.1	mother, father	"	2.204	2.582	2.324	1.422
16	P.L.	M	16	1.3	brother	monozyg.	2.391	2.450	2.033	1.589
17	M.L.	F	11	1.5	0	"	1.146	2.435	1.699	1.569
18	L.L.	M	12	3.0	mother etc.	"	2.691	2.883	2.525	1.487
19	H.M.	F	8	1.8	father	"	2.104	2.328	1.969	1.720
20	F.N.	M	11	1.3	mother	"	2.104	2.267	1.869	1.715
21	V.N.	F	8	2.0	"	"	1.778	2.061	1.724	1.800
22	B.O.	M	7	1.0	brother	dizyg.	2.396	2.778	2.344	1.210
23	S.R.	M	11	1.7	father	"	1.898	2.342	1.724	1.717
24	H.R.	M	16	2.1	mother	"	2.701	2.991	2.664	1.173
25	M.S.	M	11	1.8	0	"	2.182	2.589	2.526	1.199
26	M.S.	F	11	1.7	0	"	1.944	2.892	2.439	1.228
27	P.T.	M	15	2.0	father	dizyg.	2.281	2.631	2.380	1.045
28	T.T.	M	15	2.3	"	"	2.589	2.947	2.505	1.201
29	A.W.	F	11	2.1	"	"	1.929	2.519	1.643	1.596
30	B.W.	M	8	3.1	"	"	2.017	2.212	1.820	1.706
31	J.W.	F	13	1.3	"	"	2.511	2.839	2.340	1.407
32	L.M.	F	13	1.3	0	"	2.104	2.611	2.398	1.021
33	K.g.	F	13	1.5	0	"	2.238	2.864	2.490	1.097
34	C.J.	F	11	1.4	0	"	2.057	3.078	2.201	1.328
35	G.C.	F	13	1.8	0	"	2.574	2.932	2.555	1.212
36	K.H.	F	13	2.2	0	"	2.629	3.072	2.710	1.130
37	B.B.	F	11	1.7	0	"	2.111	2.720	1.875	1.573
38	H.G.	F	12	1.2	0	"	1.697	2.462	1.966	1.498
39	L.g.	F	13	1.8	0	"	2.369	3.013	2.386	1.279
40	A.v.E.	F	11	1.3	0	"	2.057	2.756	2.305	1.319
41	G.E.	F	9	1.7	sister	"	2.199	2.602	2.340	1.290
42	K.F.	F	16	1.2	mother	"	2.215	2.831	2.288	1.433

Fig. 1. Representation of the analogue computer parameters of the glucose infusion test. Arrows denote the parts of the insulin curve influenced by the parameters. k_g influences the total glucose curve. From Cerasi and Luft (1967a)

tained in healthy subjects. The parameter values presented in this paper are logarithmic transformations. For the sake of brevity, k_{11} is used instead of $\log k_{11} 10^3$, k_{12} instead of $\log k_{12} 10^2$ and k_g instead of $\log k_g$.

Results

All children had normal k -values with a mean of 1.8 ± 0.5 . The fasting blood glucose concentration was normal, and there was no glucosuria.

The computer parameter values are given in Table 1. It follows that k_{11} – measuring the initial insulin response – in seven subjects was equal to or lower than 1.8 which was previously chosen as the arbitrary lower border in normal adults (Cerasi and Luft, 1967a).

In Fig. 2, a to d, the distributions of the various computer parameters in this material are compared

with the distributions found in adults (Cerasi and Luft, 1967a). It is seen that the parameter values had a similar distribution in the groups of children and

adult subjects. This similarity is stressed by the comparison of mean values for the different parameters: k_{11} was 2.163 ± 0.348 in children and 2.128 ± 0.434 in

Fig. 2. (a to d) Frequency distribution of the computer parameters in the group of children (dotted bars) superimposed on the distribution histograms of the adult control group (lower histograms). Adult diabetic subjects in the upper histograms

adults, k_{12} 2.634 ± 0.261 and 2.744 ± 0.255 , b 2.170 ± 0.322 and 2.173 ± 0.315 , k_g 1.440 ± 0.241 and 1.484 ± 0.209 respectively, all differences being non-significant.

Fig. 3 gives examples of different types of insulin response during glucose infusion in the present material of children. As can be seen, a normal glucose

Fig. 3. Examples of different types of insulin response to glucose infusion in children with normal glucose tolerance

tolerance could be accompanied by marked differences in insulin response. The test in subject H. G. demonstrates an insulin response characteristic for diabetic and prediabetic adult subjects.

Discussion

We have previously focused attention on the possibility of a delayed and diminished insulin-releasing capacity of the beta-cells of the pancreas being primary event in the pathogenesis of genetic diabetes (Cerasi and Luft, 1967c). This has also been discussed by other authors (Jahnke *et al.*, 1966; Colwell and Lein, 1967; Shima and Foa, 1967; Daweke *et al.* 1968). The studies from which the hypothesis was derived were performed on adult subjects. The abnormal insulin response found in these adults could either have been present from infancy or have developed at some later stage as a consequence of other genetic factors.

Obviously newborns should be studied in this regard. However, it has been shown that the newborns of healthy mothers have a limited capacity to secrete insulin, which is corrected at about four weeks of age (Baird and Farquhar, 1962; Milner and Hales, 1965;

Pedersen *et al.*, 1966; Slone *et al.*, 1966; Spellacy *et al.*, 1967). Therefore, newborns are unsuitable for such an investigation. For obvious practical reasons we have preferred to use the glucose infusion test in children of an older age group, 7–16 years.

The results obtained show clearly that decreased insulin response together with normal glucose tolerance does occur in children, at least from the age of seven years. This might support our suggestion that the low and delayed insulin response to glucose probably is an inherited factor. For a definite proof these studies should be extended to infants.

Although some of the children were siblings, the present material is far too small to allow any discussion on the mode of inheritance of the type of insulin response.

Subjects nos. 6 and 18 were monozygotic twin brothers of diabetics. No. 6 demonstrated the typical prediabetic type of insulin response. This is in accordance with our previous findings in adult monozygotic twin sibs of diabetics (Cerasi and Luft, 1967b). The insulin response in subject no. 18 was completely normal. This might indicate – unless diabetes in the twin sib was not of genetic nature – that the type of insulin response to glucose infusion can be discordant in some identical twins.

One would expect *a priori* a higher occurrence of low insulin response in this material since a family history of diabetes occurred in the majority of instances. However, it should be remembered that we were unable to demonstrate any increase in the occurrence of diabetes in the families of adult subjects showing impaired insulin response to glucose (Cerasi and Luft, 1967d).

The pertinent literature gives very limited information on the insulin response to glucose in children. Wolfe (1967), measuring suppressible insulin by the fat pad method, found lower insulin response to an intravenous injection of glucose in children with latent diabetes than in a matched group of healthy children. The study of Poulsen *et al.* (1968), where the insulin response to oral glucose was examined in obese children and non-obese controls, does not allow any conclusions relevant to the problem stated here. Weber *et al.* (1968) gave tolbutamide intravenously to obese and non-obese children. When looking through their findings in the control group at least three out of 15 seemed to have a low insulin response to the drug. These three children might be expected to have had a diminished insulin response even to glucose, since we were able to show, in adults, a parallelism between the insulin responses to tolbutamide and to glucose (Cerasi and Luft, 1967d).

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