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Insulin response to intravenous glucagon in children with familial constitutional short stature

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Karp, M., Laron, Z., and Doron, M. (1975). *Archives of Disease in Childhood*, **50**, 805. **Insulin response to intravenous glucagon in children with familial constitutional short stature.** An intravenous glucagon test was performed in 8 children with familial constitutional short stature who were also lean. These children were randomly selected from a larger group of children with the same clinical manifestation and who had been shown to have a low insulin response to an oral glucose tolerance test and to an intravenous arginine test, without glucose intolerance. 7 out of 8 children showed a normal insulin response to intravenous glucagon, with a peak level of 53–180 μU/ml 2 minutes after the injection.

It is assumed that these insulin responses represent an intact 'rapid' pool of insulin within the β-cell, and can explain the absence of glucose intolerance in all the children so far studied.

Karp, Laron, and Doron (1973) described a group of 36 children with familial short stature who showed the following common features. Height was below the 3rd centile, skeletal age was retarded by 2 or more years, and they were lean (subcutaneous skinfold thickness of 5 mm or less). The distinct biochemical abnormalities were abnormally low insulin responses to intravenous arginine and to oral glucose in the presence of a normal growth hormone response. Despite the low insulin, no glucose intolerance was present. It was suggested that the low insulin secretion may have been related to the leanness of the body, and may have led to their reduced growth rate and slow skeletal maturation (Laron *et al.*, 1972).

The present investigation was designed to clarify the ability of these patients to secrete insulin, by measuring plasma insulin response after a single bolus intravenous injection of glucagon.

Subjects and methods

A total of 8 subjects were investigated, 7 males and 1 female (Table I). They were selected randomly from 36 subjects studied previously. The age range was 6 years 3 months—12 years 5 months. All were short, their height being −2·4 SD to −4·2 SD below the mean according to the tables of Tanner, Whitehouse, and Takaishi (1966). Most Jewish ethnic groups fall within the normal limits of these charts (Laron, 1968). All subjects were lean, with a subscapular skinfold thickness of 5 mm or less. 7 were of oriental Jewish origin.

All tests were performed on an ambulatory basis after an overnight (12– to 14–hour) fast. Before the tests all the subjects were given their regular diet, which contained at least 250 g carbohydrates per day. An indwelling needle was inserted into the antecubital vein and the patient then rested in a recumbent position for one hour before the start of the test. The intravenous glucagon test was performed by injecting crystalline glucagon (Eli Lilly & Co.) 0·03 mg/kg rapidly in 2 to 4 seconds. Blood was withdrawn for glucose, insulin, and growth hormone at 0, 2, 5, 10, 20, 30, 40, 50, 60, 90, and 120 minutes. Blood glucose was determined on the day of the test with the Technicon Autoanalyser. Plasma insulin was assayed by a double-antibody radioimmunoassay using a modification of the method of Hales and Randle (1963). Plasma growth hormone was assayed by radioimmunoassay using a charcoal modification of a previously described method (Laron and Mannheimer, 1966). Control values for each test were obtained by examination of endocrine healthy, nonobese children and adolescents.

Results

Table II summarizes the effect of the intravenous injection of glucagon. Fasting blood sugar ranged between 76 and 97 mg/100 ml; a slight rise was seen after 5 minutes and a peak ranging from 110

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TABLE I

Pertinent clinical data of 8 children with familial constitutional short stature

Case no.	Sex	Age (yr) (m)	Height (SD)	Skinfold (mm)		Country of origin of father
				Iliac	Subscapular	
1	M	12 5	−2·4	5	3	Morocco
2	M	9 5	−3·1	5	5	Iraq
3	M	8 9	−4·2	3	3	Yemen
4	M	6 3	−3·3	3	4	Yemen
5	M	11 5	−2·9	5	6	Morocco
6	M	9 3	−3·1	4	4	Yemen
7	M	8 6	−2·5	5	5	Israel
8	F	9 1	−3·3	5	6	Morocco

to 167 mg/100 ml occurred after 20 to 40 minutes. However, plasma insulin rose rapidly from the low fasting levels. In 7 out of the 8 children a significant peak (54 to 180 μU/ml) was observed at 2 minutes after the injection, slowly decreasing thereafter to starting values between 30 and 60 minutes. Only one subject (Case 4) had a low (36 μU/ml) and delayed (60 min) insulin peak.

With the exception of Case 5, all had low to normal plasma growth hormone concentrations at the start of the test. The peak time occurred between 20 and 40 minutes in 5 children, and was delayed (120 min) in 2. In Case 5 who had a high fasting value, a plateau was reached, followed by a decrease to normal values between 50 and 60 minutes followed by a second peak at 120 minutes.

Table III shows a comparison of the peak insulin levels obtained in the previous study during intravenous arginine, oral glucose tolerance test, and intravenous glucose tolerance test (IVGTT) with the results from the present study. With one exception the overall insulin response to intravenous glucagon was greater than the insulin response obtained during arginine infusion, and during oral or intravenous glucose tolerance. When compared to the peak in IVGTT at 2 minutes, the insulin peak during intravenous glucagon was higher in 5 patients, the same in 1 and lower in 1. The Fig. shows the comparative response in 3 children (Cases 2, 6, 8, respectively).

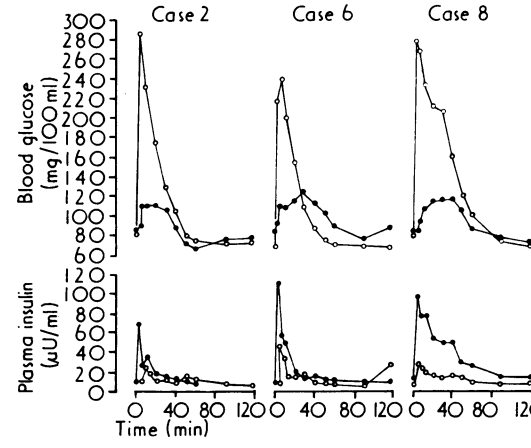

FIG.—*Glucose and insulin response to intravenous glucose* (○) *and intravenous glucagon* (●) *in 3 cases (2, 6, 8) with familial constitutional short stature.*

TABI

Blood glucose, plasma insulin, and growth hormone responses to intraven

Case no.	Blood glucose (mg/100 ml)											Plasma ins				
	Minutes											Min				
	0	2	5	10	20	30	40	50	60	90	120	0	2	5	10	20
1	90	92	96	109	129	137	124	105	97	90	91	11	180	101	60	38
2	84	88	108	108	110	106	86	70	64	78	76	8	67	25	34	19
3	76	88	94	106	110	116	104	96	82	80	82	8	57	35	20	11
4	97	97	103	115	129	149	167	167	—	133	86	4	6	9	16	18
5	83	86	103	119	130	120	120	102	93	76	80	7	54	40	38	19
6	82	88	106	106	114	122	111	100	87	75	85	8	108	55	48	19
7	90	90	102	110	116	115	94	64	74	64	71	8	53	34	—	17
8	81	81	90	104	112	113	114	103	82	76	72	13	94	74	75	52

TABLE III

Comparison between peak plasma insulin levels during intravenous arginine, oral glucose tolerance test (GTT), intravenous glucose, and intravenous glucagon in children with familial constitutional short stature

Case no.	Peak insulin (μU/ml)			
	Arginine	Oral GTT	GTT*	Glucagon*
1	15	41	11	180
2	25	34	26	67
3	11	23	54	57
4	10	20	59	36
5	16	27	42	54
6	22	19	45	108
7	18	45	—	53
8	23	30	28	94
Normal children and adolescents (mean ± SD)	n = 41 56 ± 47	n = 53 101 ± 60	n = 6 60 ± 15	n = 14 88 ± 58

*At 2 minutes, except Case 2 where at 5 minutes.

Discussion

In contradistinction to the low insulin response to arginine and the oral glucose tolerance test in children with familial constitutional short stature, bone age retardation, and lean body, we found a normal insulin response to intravenous glucagon in 7 out of 8 children tested. When comparing these responses with the insulin rise at 2 minutes during an IVGTT, it was found that only 2 children (Cases 3 and 4) had a normal insulin response, 2 (Cases 5 and 6) had a relatively low response and 3 (Cases 1, 2 and 8) a markedly low insulin response; thus showing the marked difference between the stimulation of the β-cells of these patients with glucagon on the one hand, and with glucose (oral or IV) on the other. The difference was further proven when comparing the glucose concentrations to the concomitant insulin response. It was clearly seen (Fig.), that the insulin response is not related to the level of blood glucose, which was much higher after the glucose injection than after the glucagon injection. Glucagon injection induces a rapid insulin response in healthy subjects (Samols, Marri, and Marks, 1965) probably by a direct stimulation of the pancreas (Devrim and Recant, 1966). This was further corroborated from the present study.

Further evidence for a different mechanism of action of glucose and glucagon on the β-cell is that in diabetic children requiring exogenous insulin it was shown that intravenous glucagon can elicit a positive insulin response which is, however, shorter and lower than in controls (Chiumello, Del Guercio, and Bidone, 1968; Weber, 1975).

The low insulin response to oral GTT in the children we studied was in the range observed in our clinic in children with juvenile type diabetes.

The main difference was the absence of glucose

ucagon (0·03 mg/kg) in children with familial constitutional short stature

I/ml)				Plasma growth hormone (ng/ml)										
				Minutes										
50	60	90	120	0	2	5	10	20	30	40	50	60	90	120
18	14	10	10	7·1	4·0	3·4	3·8	2·3	1·4	1·4		1·0	18·9	17·8
7	5	—	—	1·0	1·0	1·3	7·4	14·0	13·0	13·0		5·5	3·0	13·4
9	6	8	8	1·0	1·0	2·0	5·2	9·0	8·7	7·3		3·0	1·0	1·4
26	36	19	5	1·1	5·5	6·3	9·5	11·3	8·3	4·6		2·3	1·8	1·0
10	9	6	5	20·9	21·1	21·9	17·9	16·9	10·9	7·3	4·5	3·8	13·1	13·3
10	9	7	8	2·4	2·2	1·9	3·7	6·4	10·1	11·8		11·1	4·9	2·0
7	9	9	6	3·3	7·9	12·1	13·3	15·2	12·0	6·8		3·1	1·7	6·1
27	22	11	12	2·7	2·2	2·2	2·4	1·8	1·0	1·1		1·6	1·5	13·2

intolerance. According to the concept of two compartmental systems for insulin release in the β-cell (Porte and Pupo, 1969), there exists a small storage pool which responds to rapid changes in blood glucose, and a larger pool responding to a prolonged stimuli. The 'rapid' pool is considered to control the rate of peripheral glucose utilization (Lerner and Porte, 1971), while the second pool represents the function of pancreatic reserve. The positive insulin response to glucagon in the children described by us may show that the 'rapid' pool is intact, therefore explaining the lack of glucose intolerance. A relatively low glucagon response to intravenous arginine found in these children may also explain the relative insulin sensitivity (Josefsberg *et al.*, 1974).

Further studies are required to determine whether the difference in response between glucose and glucagon of the β-cells in some patients with constitutional growth retardation is due to a cell receptor alteration.

All the children tested showed a rise in plasma growth hormone after the glucagon injection. The pattern of the response was not uniform, and the time of the appearance of the peak levels was variable, as reported by others (*British Medical Journal*, 1973). This pattern of response excludes a primary role of growth hormone in the insulin response.

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