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Insulin Secretion in Down's Syndrome

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Summary. Insulin secretion after oral (100 g) and i.v. glucose (0.33 g/kg b.w.) was studied in 14 patients with 21-trisomy (Down's syndrome) and in 18 normal subjects. Plasma immunoreactive insulin (IRI), fasting and at predetermined time intervals during each glucose load, was measured by a double antibody method (Hales-Randle). Tolerance to oral glucose in Down's patients was found to be normal though a flat, late peaked glycaemic response was characteristic of the group. Fasting IRI and insulin levels after oral glucose in patients did not significantly differ from those in the normal group. After i.v. glucose, the patients showed a slower decline of the blood sugar, maintaining significantly higher levels than the normals at 30, 40, 50 and 60 min after the glucose load. However, the peripheral glucose uptake expressed by the K index (Conard) did not significantly differ from the normal despite the lower K values in the patients. Insulin release after i.v. glucose showed some differences between both groups. — The present study cannot support a causal relationship between D.M. and the 21-trisomy through an altered insulin secretion.

Key words: Normal group. Down's syndrome, mongoloid patients. Oral glucose tolerance test. Intravenous glucose tolerance test. Blood glucose. Immunoreactive insulin.

Introduction

The prevalence of Diabetes Mellitus (D.M.) in patients with Down's syndrome has been observed to be higher than in the general population [1, 2]. A logical approach to this problem is to study the beta cell function in patients with Down's syndrome. In this communication we report the results obtained in the study of insulin secretion in a selected population of such patients.

Material and Methods

Material: The group of patients included 14 clinically and cytogenetically proven cases of Down's syndrome (primary 21 trisomy). All patients were attending a specialized institution on a part-time basis. None of them had a family history of D.M. The control group was composed of 18 healthy, nonobese, nondiabetic subjects with no family history of D.M. The characteristics of both groups are summarized in Table 1. A close matching between them was only possible with respect to age and sex.

Methods: Oral glucose tolerance test (O.G.T.T.) and rapid intravenous glucose tolerance test (I.V.G.T.T.) in patients and in normal subjects were performed exactly as described previously [3]. The O.G.T.T. was evaluated as proposed by Fajans and Conn [4] and the I.V.G.T.T. interpreted according to the K values as described by Conard [5]. Any drug therapy was discontinued in patients a week before each test. Blood glucose (B.G.) was assayed in duplicate by the Hoffmann ferricyanide method adapted to the Technicon Autoanalyzer [6]. Plasma immunoreactive insulin (I.R.I.) was assayed in duplicate by the double antibody method of Hales and Randle [7]. The significance of the differences between mean values in both groups was analyzed by Student's t test.

Results

Mean values for B.G. and plasma I.R.I. during O.G.T.T. and I.V.G.T.T. in both groups are presented in Table 2. *O.G.T.T.*: as shown in the upper part of the table, the response in patients to the 100 g oral glucose load was well within the adopted criteria of normality [4]. However, the blood sugar levels in the patient group were significantly higher than those in the normals at 90 ($p < .005$) and 120 ($p < .0005$) min after the glucose load. By contrast, I.R.I. response pattern in both groups was closely similar, with no statistically significant differences at any time interval. *I.V.G.T.T.*: B.G. values in the patient group were significantly higher (lower part, table 2) than in the normals at: 30 ($p < .05$), 40 ($p < .001$), 50 ($p < .001$) and 60 ($p < .002$) min after I.V.G.T.T. (.33 g glucose/kg body wght.). K values ($\bar{X} \pm$ S.E.M.) were also lower in patients ($K = 1.57 \pm 1.4$) than in normals ($K = 1.72 \pm 1.2$), but the differences were not statistically significant ($p < .10$).

I.R.I. values at fasting were similar in both groups, but the patients showed a secretory pattern different from that in the normal group. In fact, mean I.R.I. levels after i.v. glucose in the patients were significantly higher at 50 ($p < .05$) and 60 ($p < .0025$) min.

Discussion

Tolerance to glucose in Down's syndrome has been repeatedly studied [2, 8] but simultaneous investigation of insulin secretion is seldom encountered in the literature [9, 10]. In older studies, thoroughly reviewed

by Benda [11], qualitative and/or quantitative abnormalities of carbohydrate tolerance in patients with Down's syndrome were reported. However, most of these studies lacked uniform criteria in the selection of patients as well as in the performance and interpretation of the tests. More recently, Milunsky [2, 12] has re-examined this problem with a very strict methodological approach. Using epidemiological criteria, Burch and Milunsky [13] suggested the hypothesis that an auto-immune damage of the pancreatic beta cell could underlie the peculiar affinity of D.M. for the patients with Down's syndrome. However, studies by Milunsky, Marks and Samols [9] and by Milunsky and others [10] failed to uncover definite abnormalities in the insulin response to i.v. glucagon and oral glucose. In our patients only minimal modifications in carbohydrate tolerance and insulin secretion were discovered. During O.G.T.T. no truly abnormal glycaemic response was present in individual patients, but a flat and late peaked glycaemic curve characterized the group. In agreement with the above mentioned studies [10] no abnormalities in insulin release were found after the oral glucose load. With the I.V.G.T.T. a relatively decreased glucose utilization, with a more persistent insulin release, was present in the patient group. These findings could perhaps suggest some kind of peripheral resistance to insulin action, but it should not be forgotten that the underdeveloped body mass of the

Table 1. *Patients and Normal subjects. Characteristics of both groups*

	N	Sex		Age (years)	Body weight (kg)	Height (cm)	Body surface (sqm)
		F	M	Mean (range)	Mean ± S.E.M. (range)	Mean ± S.E.M. (range)	Mean ± S.E.M. (range)
Normal group.	18	6	12	21 (16–26)	66.5± 2.2 (52 –82)	1.71±1.8 (1.57–1.82)	1.77±3.7 (1.54–2)
Patients	14	6	8	18 (13–24)	49.7± 3.5 (31 –68)	1.49±1.9 (1.38–1.61)	1.41±6 (1.11–1.72)

Table 2. *Blood glucose (B.G. mgs%) and Plasma Immunoreactive Insulin (I.R.I. μU/ml) in normals and Down's patients during O.G.T.T. (100 g of glucose) and I.V.G.T.T. (.33 g glucose/kg body weight). Values are* X ± S.E.M. *Number of subjects in parentheses*

Time: minutes

Test	Group	Determinations	0	15	30	60	90	120
O.G.T.T.	Normals	B.G. (mg%)	78.2 ±1.5 (18)	92.1 ± 2.7 (18)	112.8 ± 4.2 (18)	105.4 ± 4.5 (18)	85.1 ± 3.8 (18)	79.3 ± 1.6 (18)
		I.R.I. μU/ml	24.9 ±3.4 (11)	56.7 ± 6.2 (12)	114.2 ±13.9 (12)	147.1 ±18.2 (10)	113.5 ±14.4 (12)	87.0 ±13.5 (11)
	Down's patients	B.G. (mg%)	79.3 ±2.6 (14)	95.5 ± 3.6 (14)	112.2 ± 7.9 (14)	108.0 ± 7.6 (14)	100.5 ± 4.0 (14)	95.8 ± 3.5 (14)
		I.R.I. μU/ml	29.6 ±3.1 (14)	81.9 ±18.9 (10)	134.0 ±24.1 (13)	135.1 ±24.1 (14)	146.0 ±24.9 (11)	114.2 ±21.9 (9)

Test	Group	Determinations	0	5	10	20	30	40	50	60
IVGTT	Normals	B.G. (mg%)	77.2 ±1.5 (18)	263.11 ± 9.6 (18)	181.5 ±10.7 (18)	129.1 ± 4.6 (18)	99.5 ± 4.2 (18)	88.5 ± 3.8 (17)	80.7 ±3.6 (17)	73.6 ±2.5 (18)
		I.R.I. μU/ml	26.6 ±3.01 (15)	103.7 ±15.3 (14)	92.4 ±12.7 (15)	69.6 ±10.0 (15)	56.6 ± 5.9 (14)	49.4 ± 5.7 (13)	38.6 ±6.2 (13)	28.9 ±3.6 (14)
	Down's patients	B.G. (mg%)	78.6 ±2.6 (13)	211.4 ±21.7 (10)	186.4 ±10.5 (11)	141.0 ± 9.9 (12)	115.3 ± 5 (11)	111.0 ± 7.4 (13)	103.4 ±7.5 (12)	97.7 ±7 (13)
		I.R.I. μU/ml	28.7 ±2.5 (10)	138.4 ±21.7 (10)	104.8 ± 4.3 (7)	70.5 ± 5.9 (9)	77.6 ±11.4 (9)	65.8 ±10.2 (8)	55.0 ±5.5 (9)	57.3 ±8.2 (10)

Down's patients could be an important factor in determining those subtle differences from the normal population. Therefore, our present results do not reveal any clearcut impact of the genetic imbalance caused by the 21-trisomy upon the functional capacity of the beta cell that could be linked with the high incidence of D.M. in that disease.

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