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Glucose Intolerance in Uraemia

II. Plasma Growth Hormone and Glucagon Values

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Summary. This study confirms our first results showing large and prolonged insulin secretion in patients with azotaemia and glucose intolerance. It shows that the pattern of growth hormone and glucagon secretions was not modified in these well nourished patients with chronic renal diseases and hyperazotaemia: the fasting values were in the normal range and the response during a 5 h glucose tolerance test was normal, except in one man with Fabry's disease, in whom a very large increase in plasma growth hormone was observed at the beginning of the GTT when the blood glucose increased. There was no increase in plasma H.G.H. during the intravenous glucose tolerance test of 60 min. Plasma glucagon values were normal. — This study done on 11 subjects shows that the diminished tolerance to glucose observed in azotaemic patients in presence of a large and prolonged insulin secretion cannot be related to abnormalities in growth hormone or glucagon secretion.

Intolérance au glucose dans l'urémie. II. Valeurs plasmatiques de l'hormone de croissance et du glucagon

Résumé. Cette étude confirme nos premiers résultats démontrant une sécrétion d'insuline importante et prolongée chez des patients présentant une azotémie élevée et une intolérance au glucose. Elle montre que les caractéristiques des sécrétions d'hormone de croissance et de glucagon ne sont pas modifiées chez ces patients bien nourris qui présentent des maladies rénales avec hyperazotémie: les valeurs à jeun sont dans les limites normales et la réponse au cours d'un test de tolérance au glucose d'une durée de 5 h est normale, excepté chez un homme ayant une maladie de Fabry chez lequel une très importante augmentation de l'hormone de croissance dans le plasma a été observée au début du GTT lorsque le glucose du sang s'élevait. Il n'y a pas d'augmentation d'hormone de croissance dans le plasma pendant le test de tolérance au glucose de 60 min. Les valeurs du glucagon plasmatique sont normales. — Cette étude effectuée sur 11 sujets montre que la diminution de la tolérance au glucose qui est observée chez les patients azotémiques en présence d'une sécrétion d'insuline importante et prolongée ne peut pas être mise en relation avec des anomalies de sécrétion de l'hormone de croissance ou du glucagon.

Eingeschränkte Glucosetoleranz bei Urämie. II. Plasma-Spiegel von Wachstumshormon und Glucagon

Zusammenfassung: Die vorliegende Untersuchung bestätigt unsere früheren Resultate, die bei Patienten mit Urämie und Störungen der Glucosetoleranz eine ausgeprägte und verlängerte Insulinsekretion zeigten. Sie ergibt ferner, daß das Verhalten der Sekretion von Wachstumshormon und Glucagon bei diesen Patienten mit chronischen Nierenerkrankungen, die sich in gutem Ernährungszustand befinden, nicht verändert war: Die Nüchternwerte lagen im Normbereich und während eines 5stündigen Glucosetoleranztestes kam es zu einer normalen Reaktion, wenn man von einem Mann mit Fabry'scher Erkrankung absieht, bei dem zu Beginn des GTT während des Blutzuckeranstieges eine sehr starke Zunahme des Wachstumshormons festzustellen war. Während des einstündigen i.v. GTT stieg das Plasma H.G.H. nicht an. Die Plasma-Glucagonspiegel verhielten sich normal. — Diese Untersuchungen an 11 Probanden zeigen, daß die verringerte Glucosetoleranz bei urämischen Patienten bei gleichzeitig verstärkter und verlängerter Insulinausschüttung nicht auf eine gestörte Sekretion von Wachstumshormon oder Glucagon zurückgeht.

Key-words: Diabetes, uraemia, growth hormone, glucagon, insulin.

The occurrence of glucose intolerance in patients with renal failure is now well known [6—9, 11, 14—16, 18, 21, 22, 25, 27, 28]. We have shown that the insulin secretion is important and prolonged in azotaemic subjects submitted to oral glucose tolerance tests [25]. These results were confirmed by others [6, 7, 9]. Despite the large insulin secretion no reactive hypoglycaemia was observed in the late phase of the oral glucose tolerance test. This might suggest that there is also a high secretion of growth hormone and/or glucagon in patients with uraemia. We have studied 11 new uraemic subjects in respect to growth hormone and glucagon secretion.

Methods

Six men and five women were studied. All were well-nourished, chronically hyperazotaemic subjects (blood urea nitrogen above 100 mg/p.100 ml). They were between 20 and 67 years old, with a mean of 45. None were obese. There was no family history of diabetes or obesity. Seven were submitted to an oral glucose tolerance test (GTT) by giving them 45 g of glucose per m^2. On 5 subjects a rapid intravenous glucose tolerance test (25 g per m^2) was performed, and three of them received a simultaneous injection of 2 μg/kg of glucagon. One arginine infusion test (25 g in 400 ml H_2O in 30 min) was also performed.

Blood glucose was determined by the glucose oxidase method [12] using Boehringer commercial kits (C.F. Boehringer & Soehne GmbH., Mannheim). Plasma insulin, growth hormone (H.G.H.) and glucagon were estimated by the BERSON and YALOW radioimmunological method [4], as first employed for insulin [29], with small modifications used in our laboratory and previously described for insulin [19, 20], H.G.H. [24], and glucagon [2]. The standard now used for H.G.H. is the purified preparation of Prof. A.E. WILHELMI (Atlanta, Georgia) HS 705 (2 I.U./mg). HS 705 is biologically and immunologically twice as potent as HS 545 A, a preparation we have previously used [24].

The pattern of plasma growth hormone does not seem to be modified in these hyperazotaemic subjects. No high, fasting values were observed, except in patient LEC... A secondary increase in plasma H.G.H. was seen in 5 out of 7 subjects during the 5 h GTT. An initial small increase, probably non-specific, was seen in 2 patients. A good response to arginine was observed in the one case studied. During the intravenous glucose tolerance test only one secondary increase in plasma H.G.H. was observed, probably because of the diminished rate of glucose disappearance and the short period of observation (Table 2).

Table 1. *Oral glucose tolerance tests performed on seven azotaemic patients*:

Case		0 min	30 min	60 min	120 min	180 min	240 min	300 min
DUR...	a)	106	138	159	144	121	75	82
	b)	19	144	116	92	46	34	26
	c)	2.5	4.0	2.5	2.5	9.0	13.0	10.0
	d)	2.2	2.5	2.5	2.0	2.0	2.4	2.2
GRA...		101	163	161	174	147	129	79
		75	200	260	260	280	165	62
		6.0	2.5	3.5	4.0	3.0	3.5	6.5
		2.0	1.5	1.7	1.9	1.7	1.7	1.7
HAT...		120	188	290	258	195	98	63
		19	70	75	130	110	38	34
		2.0	4.0	9.5	3.5	1.5	2.2	6.5
		—	—	—	—	—	—	—
LEC...		80	144	124	72	92	80	80
		18	400	210	28	30	25	24
		13.5	10.0	28.0	16.0	7.0	1.0	0.5
		2.2	1.8	—	1.4	1.3	1.4	1.6
NEV...		78	104	126	104	100	68	—
		64	50	125	100	78	21	—
		2.5	3.5	7.5	2.0	0.8	5.5	—
		2.7	3.2	2.5	2.1	2.0	—	—
SUI...		104	128	112	68	92	80	80
		20	100	84	24	30	18	24
		0.5	0.5	4.5	8	14.0	11.0	0.5
		—	—	—	—	—	—	—
SYL...		104	184	212	96	100	88	88
		16	78	78	78	40	25	22
		1.0	0.1	2.0	0.1	2.0	3.0	1.0
		1.8	2.7	1.5	2.3	2.6	2.9	1.6

a) first value: blood glucose in mg per 100 ml
b) second value: plasma insulin in μu/ml
c) third value: plasma H.G.H. in ng/ml
d) fourth value: plasma glucagon in ng/ml

There was no hypersecretion of H.G.H. which could be responsible for the apparent resistance to insulin.

In only one subject (LEC...) was a very special pattern in H.G.H. secretion observed during the glucose tolerance test. Plasma H.G.H. was very high before the glucose tolerance test, and a large rise occurred during the first hour after the glucose load. It may have been due to a non-specific increase in plasma H.G.H., since it can occur spontaneously in normal

Results and Comments

The levels of blood glucose, of plasma insulin, of plasma growth hormone, and of glucagon following a glucose tolerance test are given in Table 1. During the intravenous glucose tolerance test the results obtained are given in Table 2.

adolescents [13] or in normal, fasting adults [17], [10]. Patient LEC... had Fabry's disease [5, 23]. In this inherited, systemic metabolic disease (glycolipid lipidosis), characterized by an accumulation of two or more neutral glycolipids in the tissues, hypothalamic deposits were described [23]. It may be speculated that in this subject the rise in plasma H.G.H. one hour after glucose may be related to hypothalamic disorders, since it was observed in two adults with acromegaly and in one child with an optic glioma that encroached upon the hypothalamus [3]. In patient LEC... a complete autopsy was not available, and no answer can be given to this hypothesis.

The plasma glucagon values were in the normal range in the fasting period, and during GTT or the other investigations (Table 1 and 2)

Table 2. *Rapid intravenous glucose tolerance tests on five azotaemic patients:*

Case		Time in minutes								
		0	2	5	7	10	20	30	60	90
GEO...	a)	75	277	254	237	228	213	181	115	74
	b)	24	160	126	100	150	100	84	40	27
	c)	1.5	2.5	2.5	2.5	2.5	4	3.6	2.5	1.2
	d)	—	—	—	—	—	—	—	—	—
GRA...		90	—	—	—	282	230	206	144	—
(X)		25	—	>400	—	>400	220	145	150	—
		5	—	4	—	5	3.5	3	5	—
		1.20	—	1.40	—	1.50	1.40	1	1	—
PAI...		80	268	274	260	260	258	250	200	—
		8	62	62	58	62	64	62	62	—
		4	3.2	3.2	3.6	4.5	3.2	3.2	3.6	—
		—	—	—	—	—	—	—	—	—
SAB...		65	262	246	240	240	228	204	179	160
		—	—	170	96	125	150	92	58	40
		< 0.6	< 0.6	< 0.6	< 0.6	<0.6	< 0.6	4	4.5	4
		—	—	—	—	—	—	—	—	—
SYL...		113	—	254	—	234	—	193	161	113
(▲)		20	—	40	—	36	—	22	25	18
		5	—	5	—	3.5	—	3	1.5	4
		1.80	—	1.50	—	1.55	—	1.25	1.40	2

Cases GEO..., PAI... and SAB... received simultaneously 2 μg glucagon per kg body weight, and the I. V. glucose.
Symbols (X) and (▲) indicate subjects also submitted to oral GTT (Table 1)*:*
a) first value: blood glucose in mg per 100 ml
b) second value: plasma insulin in μu/ml
c) third value: plasma H.G.H. in ng/ml
d) fourth value: plasma glucagon in ng/ml

The plasma glucagon values were in the normal range in the fasting period, and during GTT or the other investigations (Table 1 and 2)

Discussion

This study done on 11 subjects with chronic renal deficiency confirms our first study [25], which has shown that the insulin secretion is generally considerable and prolonged[1] in azotaemic subjects submitted to oral glucose tolerance test, a fact also confirmed by others [6, 7, 9].

This study also shows that the glucose intolerance observed in patients with renal failure cannot be related to elevated plasma levels of growth hormone or glucagon either at fast or after a glucose load.

The actual mechanism(s) of the diminished tolerance to glucose in hyperazotaemia remains unknown. We have reviewed elsewhere [26] the current hypotheses

[1] In our laboratory normal values (means ± sem) for blood glucose (BG) and plasma insulin (I) determined on 31 adults of both sexes during a 5 hour oral GTT were:

Time	0 min	30 min	60 min	120 min	180 min	240 min	300 min
BG	84.7	127.0	122.5	96.8	81.5	80.1	81.1
	±	±	±	±	±	±	±
mg/100 ml	1.6	4.0	4.3	3.5	3.0	2.8	2.0
I	13.0	68.7	74.0	51.7	25.1	13.3	8.7
	±	±	±	±	±	±	±
μu/ml	1.0	7.1	7.7	5.0	3.5	1.8	0.5

which have been advanced through publications. If one accepts that a certain degree of insulin resistance must be present, it cannot be due to a large, abnormal secretion of H.G.H. or glucagon as shown here, nor to an increase in plasma free fatty acids [9, 11], nor to acidosis [15], nor to abnormal concentrations of Na^+ or K^+ in serum [15, 21]. One study has shown improvement in glucose tolerance after administration of potassium and correction of the intra-cellular depletion of this ion [22]. The role of urea is very conflicting according to the contradictory studies: some accept [6, 14, 16], whereas others deny [11, 18, 27, 28] its responsibility in glucose intolerance. But "one might consider that even the elevated levels of insulin found in azotaemic subjects were inadequate to meet the response demanded by the elevated glucose levels; that is, the pancreatic response to the degree of hyperglycaemia present should have been even greater" [7].

In fact, two studies have shown a greater pancreatic secretion after dialysis [1, 11]. But the concept of pancreatic deficiency fails to account for the pronounced insulin response to intravenous tolbutamide [7, 25], despite the delayed nadir in blood glucose.

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