Plasma Glucagon Suppressibility After Oral Glucose in Obese Subjects With Normal and Impaired Glucose Tolerance

V. C. Borghi, B. L. Wajchenberg, and F. P. Cesar

Blood glucose, plasma insulin, and glucagon responses after a 75 g oral glucose-tolerance test were assessed in 9 normal controls, 5 obese nondiabetics (ON), 5 obese nondiabetics with fasting hyperinsulinemia (obese "resistant" nondiabetics—OR), 9 obese with impaired glucose tolerance (O-IGT), and 9 nonobese insulin-dependent diabetics (IDD). Fasting plasma glucagon concentrations were significantly higher in all groups of patients in comparison to the normal controls. Insulin secretion, evaluated in all but the IDD, was similar to normal in the ON and increased in the OR and O-IGT. Normal glucagon suppression was observed in the lean controls and ON but not in OR, O-IGT, and IDD. We suggested that the resistance to glucagon suppression after glucose load in the OR and O-IGT in the presence of increased insulin response could be an indication that the A cell participates in the relative insulin insensitivity of these subjects.

PLASMA GLUCAGON disturbances have been described in human diabetes and obesity.[1-4] Normal, exaggerated, and suppressed A cell function have been reported in these two conditions depending upon the type of patient and the method employed.

From the studies of Kalkhoff's group[2,3] it was demonstrated that the A cell is normal in obese nondiabetic subjects. Their accentuated glucagon suppression following glucose load was dependent on the level of plasma insulin secretion. On the other hand, they also confirmed that when there is an insulin deficiency there is a resistance to glucagon suppression. When both situations are associated in obese diabetics, there is an A cell insensitivity to the rising plasma glucose contingent upon deficient insulin secretion.

It should be of interest to evaluate the glucagon response when the available insulin is antagonized in the insulin-sensitive tissues to see if the A cell participates in the whole-body insulin resistance.

A good model for such a situation is the obese nondiabetic subjects (indicated as obese "resistant" nondiabetics) and those with impaired glucose tolerance (obese IGT) both with fasting hyperinsulinemia and demonstrated to have insulin resistance.[5-7] We can compare them to obese nondiabetics with normal basal and stimulated insulin responses to the glucose load, and normal-weight, insulin-dependent diabetics with insulin deficiency (nonobese IDD).

MATERIALS AND METHODS

Thirty-seven individuals of various ages ranging from 20 to 48 years were subdivided as follows: normal controls, obese subjects presenting normal glucose tolerance (obese nondiabetics and obese "resistant" nondiabetics), impaired tolerance (obese IGT), and finally, nonobese insulin-dependent diabetics (IDD) with the duration of the disease longer than 5 years, kept on NPH insulin, from 20 to 70 U/d.

None of the normal and diabetic subjects weighed more than 10% over the ideal body weight. The obese individuals exceeded ideal body weight by 25% or more. The pertinent clinical and laboratory data on these subjects are shown in Table 1.

The criteria proposed by the National Diabetes Data Group[8] were used to classify the obese subjects. They considered obese IGT to be those with fasting venous blood glucose values < 6.7 mmol/L and two-hour blood glucose between 6.7 and 10.0 mmol/L, with one intervening value ≥ 10.0 mmol/L following a 75-g oral glucose challenge. Normal control and obese groups had negative family histories for diabetes and were receiving no medication.

All individuals had a three-day preparatory diet containing at least 300 g of carbohydrate per day. After an overnight fast and absolute bedrest for at least one hour, they were submitted to standard 75-g oral glucose tolerance test (OGTT). Diabetic subjects did not receive their insulin dose at the time of testing.

Blood samples were withdrawn from the antecubital vein at −30 minutes, and immediately before, then at 30, 60, 90, 120, and 180 minutes after the beginning of the glucose ingestion for the measurement of glucose, insulin, and glucagon levels.

For pancreatic glucagon determination, blood was placed promptly into heparinized tubes containing 0.04 mL of Trasylol (Bayer from São Paulo, Brazil; 400 Kallikrein inhibitor units per mL of blood). The mixture was immediately centrifuged at 4 °C and plasma separated and frozen until assayed.

Blood glucose was measured with a Technicon Auto-Analyzer by the ferricyanide method.[9] Plasma immunoreactive insulin (IRI),[10] and glucagon (IRG)[11] were determined by previously described radioimmunoassays (RIA).

Glucagon RIA was performed employing pork glucagon for iodination supplied by NOVO Research Institute (Bagsvaerd, Denmark) and the specific antiserum for pancreatic glucagon, RCS5, supplied by Dr S. R. Bloom. The assays were set up with standard curves made up in the laboratory control plasma prepared from pooled, time-expired blood-bank plasma, which was effectively glucagon-free.

The glucagon RIA presented high sensitivity and the useful range of the standard curve allowing measurements from 12 to at least 500 pg/mL of glucagon. The precision, evaluated through the within- and between-assays reproducibility, revealed in the first case coefficients of variation (CV) on the order of 14.9%, 5.1%, and 6.3% for the plasma samples of low (13.6 pg/mL), medium (65.3 pg/mL), and high (104.2 pg/mL) glucagon mean content respectively. In the between-assay reproducibility, CVs were 10.7%, 4.6%, and 5.6% for

From the Institute of Energetic and Nuclear Research (IPEN/CNEN-SP) and the Diabetes and Adrenal Unit, Department of Medicine, Hospital das Clínicas, São Paulo, Brazil.

Address reprint requests to Dr Vânia C. Borghi, Instituto de Pesquisas Energéticas e Nucleares (IPEN), Caixa Postal 11049, Pinheiros, São Paulo, Brazil 05508.

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Table 1. Clinical and Laboratory Data of the Study Groups

Group	Individual	Fasting Level: Glucose (mmol/L)	Fasting Level: Insulin (μU/mL)	Fasting Level: Glucagon (pg/mL)	Sex	Age (yr)	Weight (Kg)	IBW* (%)	Treatment (Insulin: U/d)
Normal controls	1	5	2	21	F	24	47.8	93	
	2	4	7	21	M	26	73.0	109	
	3	4	6	38	F	27	44.5	80	
	4	5	15	28	F	28	65.0	105	
	5	4	4	17	M	28	68.0	99	
	6	4	15	42	F	30	63.6	109	
	7	4	7	17	M	36	68.0	100	
	8	4	12	24	F	43	53.4	98	
	9	4	4	17	M	48	71.0	102	
Mean values ± SEM		4.2 ± 0.2	8.0 ± 1.6	25.0 ± 3.1		32 ± 3	61.6 ± 3.5	99.3 ± 3.0	
Obese nondiabetics	1	5	9	42	F	23	88.5	165	
	2	5	5	38	F	23	103.0	177	
	3	5	10	43	F	30	100.0	168	
	4	5	8	49	F	34	99.0	164	
	5	5	11	49	F	37	104.0	164	
Mean values ± SEM		4.9 ± 0.1	8.6 ± 1.0	44.2 ± 2.1		29 ± 3	98.9 ± 2.8	167.6 ± 2.5	
Obese resistant nondiabetics	1	5	18	77	F	23	69.0	127	
	2	6	17	129	F	28	107.0	205	
	3	6	18	100	F	28	80.5	150	
	4	6	22	87	F	29	70.7	125	
	5	5	14	105	F	31	75.0	144	
Mean values ± SEM		5.5 ± 0.2	17.8 ± 1.3	99.6 ± 8.8		28 ± 1	80.4 ± 6.9	150.2 ± 14.5	
Obese IGT	1	5	5	56	F	23	75.0	146	
	2	5	16	42	F	26	70.0	134	
	3	6	26	52	F	27	123.0	226	
	4	6	15	70	F	27	90.4	166	
	5	5	19	63	F	30	92.0	160	
	6	6	14	91	F	37	83.0	166	
	7	6	8	59	F	38	78.0	145	
	8	6	7	68	F	38	89.0	153	
	9	6	18	73	F	43	103.9	168	
Mean values ± SEM		5.7 ± 0.2	14.2 ± 2.2	63.2 ± 4.7		32 ± 2	89.4 ± 5.4	162.5 ± 8.8	
Nonobese IDD	1	10		87	M	20	52.0	86	40
	2	10		42	M	21	60.0	95	70
	3	13		49	M	23	62.0	106	50
	4	15		139	F	27	43.0	84	45
	5	9		49	F	28	51.8	94	20
	6	9		42	M	29	59.0	86	20
	7	16		118	F	31	47.0	102	35
	8	22		108	M	41	51.7	78	25
	9	9		105	M	46	63.3	96	55
Mean values ± SEM		12.5 ± 1.4		82.1 ± 12.5		30 ± 3	54.4 ± 2.3	91.9 ± 3.0	—

*IBW = Ideal Body Weight (Metropolitan Life Insurance table, 1959).

similar plasmas with glucagon mean levels of 14.6, 68.3, and 110.8 pg/mL, respectively. The precision profiles indicated that when the limit of CV is fixed to the maximum of 10%, the acceptable range for glucagon assay is 20 to 114 pg/mL and 16 to 116 pg/mL for within- and between-assays, respectively. For glucagon values in the range of 15 to 20 pg/mL the intraassay CV was of the order of 15%.[11]

Paired analysis was determined between the fasting and the lowest plasma glucagon values (nadir) after glucose.

The total integrated areas circumscribed by the glucose, insulin, or glucagon response curves to OGTT, above or below fasting baseline levels, were estimated on an IBM/370-M 155 computer, (São Paulo, Brazil) employing a trapezoidal rule. The data were expressed as mmol/L (glucose) or μU/mL (insulin) or pg/mL (glucagon) per 180 minutes, respectively.

The statistical analysis was performed by a Student's *t* test for paired and unpaired observations, defining the significance of the difference between the group means.

RESULTS

Considering that no significant differences were found between −30- and 0-minute blood glucose, plasma glucagon, and insulin levels, only the values correspondent to the samples immediately before glucose ingestion were used as the fasting level for the data analysis.

The results of blood glucose, plasma insulin (IRI),

and glucagon (IRG) concentrations during the OGTT are indicated in Fig 1.

Blood Glucose

Obese nondiabetics (ON) had the mean blood glucose levels significantly higher than control subjects at all times ($P < 0.05$) except at 30- and 180-minute samples. However, all of them were considered to have normal glucose tolerance according to the National Diabetes Data Group.[8]

The obese, resistant nondiabetics (OR) had significantly higher mean blood glucose levels than controls at all times of sampling ($P < 0.01$) except at 180 minutes. However, when compared to the ON, they only demonstrated significantly higher mean blood glucose values at the fasting and 30-minute samples ($P < 0.05$). The other group of obese subjects, glucose intolerant, had significantly higher mean glucose levels than ON and OR at all times after glucose challenge ($P < 0.01$). However, their mean fasting blood glucose concentration was significantly higher when compared to the ON ($P < 0.01$) but not in relation to the OR. The O-IGT also presented basal and postchallenge glucose mean concentrations significantly higher than the normal controls ($P < 0.001$). According to the previous reference (National Diabetes Data Group), these patients can be considered as presenting impaired glucose tolerance (IGT).

Finally, in comparison to the other groups, the insulin-dependent nonobese diabetics (IDD) presented significantly elevated fasting mean level and grossly abnormal blood glucose curves during OGTT.

Plasma Insulin

The mean basal plasma insulin levels in the normal controls and ON were similar. Mean fasting IRI values were similar in the OR and O-IGT and both of them were significantly higher than in the normals and ON ($P < 0.05$) (Table 1). The normal controls presented the mean peak plasma insulin at 60-minute samples after glucose loading. In the ON, the mean plasma insulin levels attained a plateau at 60 to 120 minutes comparable to the normal controls at all times except at 90- and 120-minute samples when they were significantly higher ($P < 0.02$).

The OR had significantly higher mean insulin values when compared to the normal controls, ON and O-IGT, after glucose challenge, at all times ($P < 0.01$) except at 30 and 180 minutes. The O-IGT group had significantly higher mean plasma IRI than the normals at 90, 120, and 180 minutes ($P < 0.01$). However, there were no significant differences in the mean

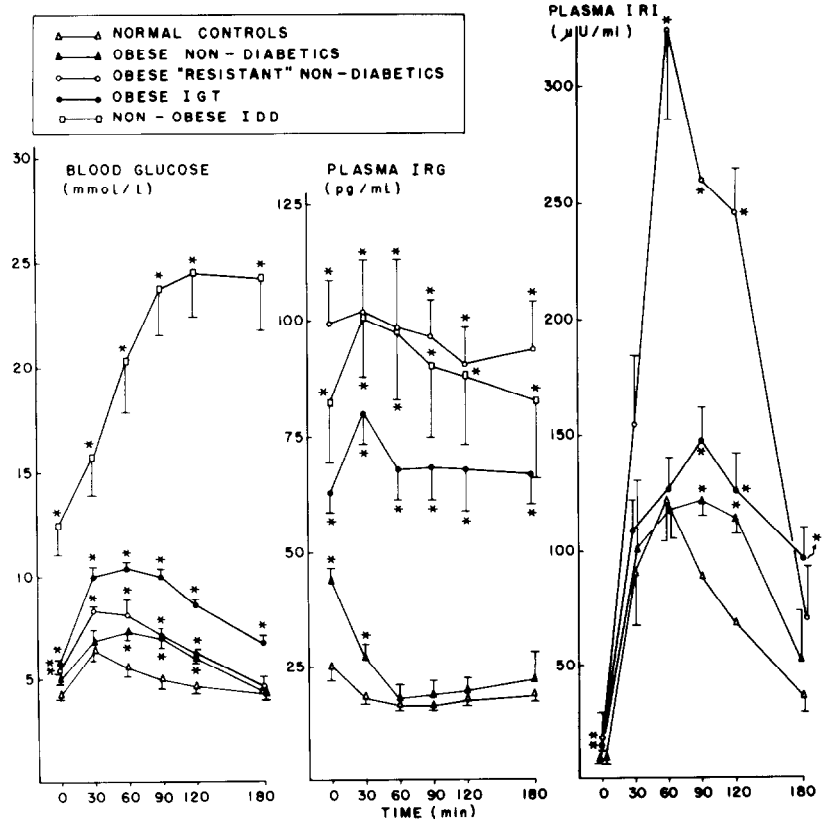

Fig 1. Blood glucose, plasma insulin (IRI), and glucagon (IRG) concentrations in nine normal, five obese nondiabetic, five obese resistant nondiabetic, nine obese with impaired glucose tolerance, and nine nonobese insulin-dependent diabetic subjects during three-hour, 75 g oral glucose tolerance test. Means ± SEM are indicated. Asterisks denote the significance of difference among mean of the normal control and other groups, $P < 0.05$.

insulin levels between the ON and O-IGT at all times of sampling after the glucose load.

Plasma Glucagon

Mean basal plasma glucagon levels were significantly higher in all groups of patients studied in comparison to the normal controls ($P < 0.01$). Within the obese subjects they were significantly higher in the OR in relation to the ON and O-IGT ($P < 0.01$). They were higher in O-IGT than ON ($P < 0.01$). However, the mean fasting levels were not significantly different when O-IGT were compared to IDD.

As expected, the normal subjects presented a progressive decrease in mean plasma glucagon levels during the first hour after glucose load. In the same way, the obese nondiabetics also presented a decrement in the glucagon levels still higher than normal at 30-minute sample ($P < 0.01$) becoming similar to the normal controls at 60 minutes and afterward.

On the other hand, the OR group had significantly higher mean plasma levels than the normal controls and ON at all times after glucose load ($P < 0.001$). However, as can be seen from Fig 1, the shape of the mean plasma glucagon curve during OGTT did not show the progressive decrease in glucagon values that actually presented an increment at the 30-minute sample. In the same way, the O-IGT presented a mean glucagon curve with a similar shape presenting values significantly higher than in the normal controls and ON at all times of sampling ($P < 0.001$). When compared to the OR, the O-IGT presented significantly lower levels at the 60-, 90-, and 120-minute samples ($P < 0.05$).

Finally, the IDD also without an evident decrease of the mean glucagon curve after the glucose challenge had significantly higher mean levels in all samples when compared to the normal subjects and ON ($P < 0.01$) but not in relation to the OR and O-IGT.

There was a positive and significant correlation between the basal plasma IRI and IRG levels in all groups studied ($r = 0.58$; $P < 0.01$), expressed by the equation: IRG = 21.05 + 2.78 × IRI (Fig 2).

The mean ± SEM fasting plasma glucagon and nadir values (lowest mean ± SEM glucagon level) after glucose load in all groups of subjects studied are shown in Table 2 where it can be seen that the normal

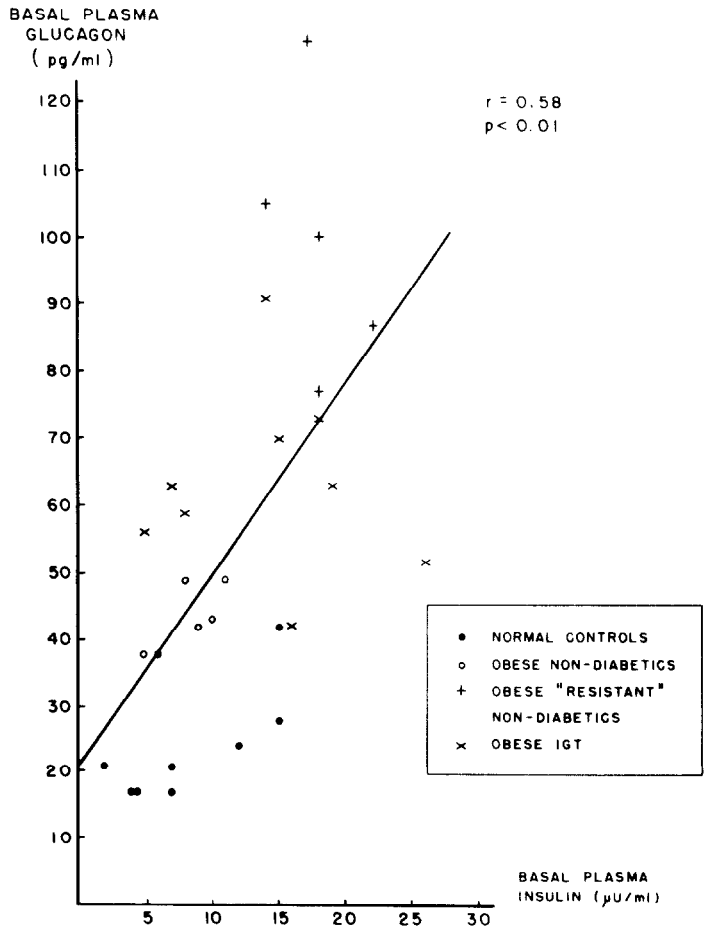

Fig 2. Relation between basal plasma insulin and glucagon levels.

Table 2. Fasting and Lowest Plasma Glucagon Levels (Nadir) During OGTT in all Study Groups

	Plasma Glucagon (pg/mL; mean ± SEM)		
Group	Fasting	Nadir	Time of OGTT
Normal subjects	25.0 ± 3.1	16.7 ± 1.3*	(60 and 90 min)
Obese nondiabetics	44.2 ± 2.1	18.0 ± 2.8†	(60 min)
Obese resistantt	99.6 ± 8.8	90.8 ± 7.6	(120 min)
Obese IGT	63.6 ± 4.6	67.2 ± 6.9	(180 min)
Nonobese IDD	82.1 ± 12.4	81.7 ± 15.8	(180 min)

*Significantly lower than fasting ($P = 0.05$).

†Significantly lower than fasting ($P < 0.001$).

controls and ON had significant glucagon suppression but not OR, O-IGT, and IDD.

Total (180-minute) Blood Glucose, Plasma Insulin, and Glucagon Responses During OGTT

Fig 3 indicates the blood glucose, plasma IRI, and IRG responses from baseline fasting levels up to 180 minutes testing period.

The mean total (180-minute) area circumscribed by the glucose response curves to OGTT above basal levels was not significantly different in the ON, OR, and normal control groups. The mean total glucose area was, however, significantly greater in the O-IGT group than in the normal control and obese nondiabetic groups ($P < 0.001$). In the IDD group the mean total glucose area, as expected, significantly exceeded the correspondent value of the other groups ($P < 0.001$).

The means of the total incremental insulin areas above basal levels were similar in the normal and ON, but significantly greater in the OR ($P < 0.001$) and O-IGT ($P < 0.05$) than in the normals. However, no significant differences were observed in the mean total insulin areas between ON and O-IGT. The OR presented significantly greater mean total insulin area than ON and O-IGT ($P < 0.001$).

The mean total integrated glucagon areas below baseline values indicated lower suppression in normal controls than in ON ($P < 0.01$). On the other hand, the OR, O-IGT, and IDD did not suppress the plasma glucagon levels during OGTT, the mean of total (incremental) glucagon areas being similar in all three groups.

DISCUSSION

There are many observations supporting the concept that the A cells are insulin sensitive (like muscle and adipocyte) and that insulin is necessary for permitting glucose entry in the A cell and subsequent inhibition of glucagon release.[12]

In obese subjects it has been demonstrated that they have insensitivity to insulin's effects on glucose metabolism in vivo[5] and in vitro.[13–15] Hatfield and his coworkers[3] demonstrated during OGTT that obese nondiabetics had a greater than normal plasma insulin secretion and plasma glucagon suppression than lean controls, whereas in the obese diabetics the lower insulin secretion was accompanied by a smaller degree of glucagon suppression in relation to the obese controls. They concluded that there was an association between the degree of plasma glucagon suppression after the oral glucose load and the briskness and magnitude of the plasma insulin response in accordance with the role of insulin release in glucose-induced glucagon suppression.[16]

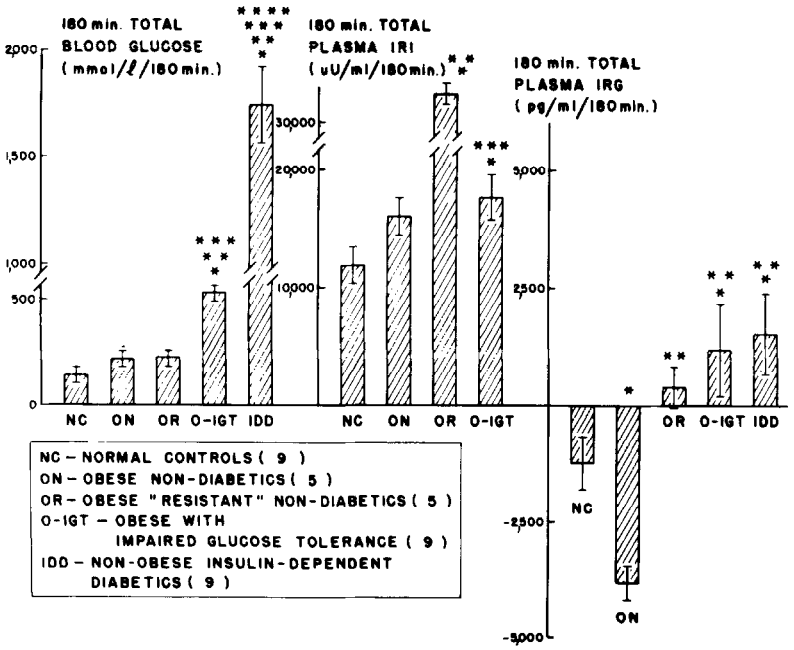

Fig 3. Total blood glucose, plasma insulin (IRI), and glucagon (IRG) responses above or below baseline concentrations during the 180-minute test period. Means ± SEM are indicated. Numbers in parenthesis are numbers of subjects in each group. * Denotes significance of the difference between means of the normal control and other groups ($P < 0.001$). ** Indicate significance of the difference between means of the ON and the other two obese groups and IDD ($P < 0.01$). * Demonstrate significance of the difference between means of the OR and the other two obese groups and IDD ($P < 0.01$). **** Demonstrate significance of the difference between means of the O-IGT and the other obese patients and IDD ($P < 0.01$).**

However, no studies were yet reported showing a perturbation of glucagon release in obese hyperinsulinemic subjects with and without impaired glucose tolerance when compared to obese nondiabetics with normal fasting IRI.

In the present study the findings of a greater than normal insulin secretion in the obese nondiabetic hyperinsulinemic group (OR) and obese-IGT would indicate that the insulin-responsive tissues are relatively insensitive to the effects of insulin on glucose uptake as previously demonstrated.[5-7] The insulin insensitivity was accompanied by the lack of suppressibility of the plasma glucagon following glucose administration when compared to the normal control and obese nondiabetic normoinsulinemic (ON) groups.

The knowledge that there is a highly significant correlation between fasting insulin level and degree of insulin resistance in human obesity[5] and our finding of also highly significant correlation between fasting insulin and glucagon levels ($r = 0.58$; $P < 0.01$) could suggest that the greater insulin resistance the higher the basal glucagon levels. In effect, it has been shown that in the well-known condition of insulin resistance, acromegaly, the high-fasting insulin concentrations are accompanied by increased glucagon levels and lack of pancreatic α-cell suppressibility following glucose load even in acromegalics without glucose intolerance.[11,17]

On the other hand, the nonobese IDD, well known to have very low residual pancreatic insulin secretion, particularly with the long duration of the disease,[18] also demonstrated lack of glucagon suppressive effect of glucose when compared to normal controls and ON. However, no significant differences were observed in total glucagon responses among IDD, OR, and O-IGT groups.

The mechanism of the lack of glucagon suppressibility in the OR and O-IGT groups could be related to the A cell resistance to the suppressive effects of insulin. However, such possibility could not be entirely accepted for the IDD group as they certainly presented absolute insulin deficiency not corrected by exogenous insulin therapy in the usual doses when the insulin levels attained at the A cell are probably far below those observed within the islets after glucose-induced insulin secretion. Weir et al[19] have indicated the importance of high intra-islet concentrations of insulin in glucose-induced glucagon suppression.

The decreased insulin sensitivity of A cells in the OR and O-IGT and the insulin deficiency of the IDD would have in common a reduced insulin effect at the A cell and its consequent lack of glucagon suppressive effect of glucose.

However, at present we should not discard the possibility of an abnormality in pancreatic somatostatin secretion, which has been described in experimental insulinopenic diabetes[20,21] but which is different from what has been shown in the obese hyperglycemic and hyperinsulinemic mouse (ob/ob).[22]

The higher mean fasting blood glucose and plasma glucagon levels associated to normal basal plasma insulin levels in the ON, when compared to the normal subjects, could be an indication of the mild degree of insulin resistance at the A cell in the ON. However, the glucose-induced insulin release would be sufficient to suppress the increased fasting glucagon levels. Because there is a continuum of insulin resistance in human obesity,[5] we would then envision a progressive parallel insensitivity of the A cell to insulin action from the ON to the OR and O-IGT, in the latter the insulin secretion after the glucose challenge being inadequate to cope with the peripheral resistance and then the development of a state of impaired glucose tolerance.

However, the interpretation of the results obtained with an oral glucose-tolerance test is more complicated than just being viewed as glucose stimulation of insulin secretion. The role of gut hormones and other factors have to be considered in the interpretation of a particular insulin or glucagon response. Furthermore, it must be considered the role of rate substrate flow as important factor(s) in the determination of fasting plasma glucagon concentration in the obese subjects independent of the insulin effects of the glucagon-secreting cells.[23,24]

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