JCI The Journal of Clinical Investigation

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J Clin Invest. 1986;77(4):1201-1206. https://doi.org/10.1172/JCI112422.

Research Article

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Insulin Action in Human Adipose Tissue in Acromegaly

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Abstract

The mechanisms underlying insulin resistance in acromegaly were investigated. Adipose tissue was obtained from nine patients with acromegaly who had in vivo insulin resistance and from 14 matched healthy control subjects. Receptor binding and the antilipolytic effect of insulin were determined in isolated fat cells. Insulin-induced glucose oxidation at a physiological hexose concentration was investigated in fat segments. In fat cells obtained from acromegaly patients after an overnight fast, insulin binding at low hormone concentrations was significantly reduced by 20–30%, insulin-induced antilipolysis was unchanged, but glucose oxidation was unresponsive to insulin. Since it has recently been observed that glucose feeding may rapidly modify insulin action in human adipocytes, fat cells were also obtained 60 min after an 100-g oral glucose load. In this situation, insulin binding at low hormone concentrations was further reduced to one-half of that in the control group, and the sensitivity of insulin-induced antilipolysis was markedly decreased in acromegaly. It is concluded that, in the fasting state, the action of insulin on glucose utilization but not on lipolysis is impaired in adipose tissue of acromegalic patients because of a postreceptor defect. After glucose ingestion, the resistance to insulin in acromegaly is further enhanced and antilipolysis is also impaired. Altered coupling between receptor and effector alone or in combination with an additional decrease in receptor binding may explain the enhancement of insulin resistance. These mechanisms may be essential factors in the pathogenesis of insulin resistance in acromegaly.

Introduction

Glucose intolerance and clinical diabetes mellitus are common manifestations of acromegaly (1, 2). Moreover, acromegaly is often associated with hyperinsulinemia (1, 3, 4) and attenuation of the glucose-lowering effect of exogenous insulin (1, 2). From these findings, it would appear that peripheral insulin resistance is of major importance for the diabetogenic effect of acromegaly. Whether this modification of insulin action in target cells occurs at the level of insulin binding or at steps distal to the hormone-receptor interaction (postbinding defect) is, however, not known. In order to distinguish between these possible mechanisms, we have presently investigated the adipocyte insulin receptor binding and the metabolic effects of the hormone on adipose tissue glucose oxidation and fat cell lipolysis in acromegaly.

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Received for publication 26 March 1985 and in revised form 3 December 1985.

J. Clin. Invest.
© The American Society for Clinical Investigation, Inc.
0021-9738/86/04/1201/06 $1.00
Volume 77, April 1986, 1201–1206

The studies on insulin resistance have so far focused on chronic alterations of insulin action that occur in the fasting state. However, it has recently been recognized that insulin action at the target tissue level can be rapidly enhanced after a physiological stimulation of insulin secretion. In human fat cells obtained from nonobese healthy subjects 1 h after an oral glucose load, insulin binding is slightly increased, and the antilipolytic effect of insulin is markedly enhanced (5). This ability of glucose to stimulate insulin action is lacking in fat cells obtained from obese, insulin-resistant subjects (6). Thus, insulin action may be rapidly modified in a physiological situation where there is a need for an enhanced insulin effect, such as after a glucose loading, and this modulation of insulin action may be involved in insulin resistance. Therefore, in the present study, insulin action in vitro was examined both in the fasted state and in connection with an oral glucose load. Subcutaneous adipose tissue was obtained after an overnight fast and 1 h after the ingestion of 100 g glucose from nine acromegalic patients who showed evidence of in vivo insulin resistance. Comparison was made with 14 control subjects, matched for age, sex, and body weight. We report here a decline in the metabolic effectiveness of insulin in acromegaly in the fasting state, which is further deteriorated after glucose ingestion.

Methods

Subjects. The study comprised nine nondiabetic patients with acromegaly, five subjects with newly diagnosed, untreated acromegaly, and four subjects with signs of active acromegaly, despite surgical intervention. The diagnosis of active acromegaly was made on the basis of clinical features plus at least one of the following criteria: (*a*) elevated basal growth hormone level; (*b*) abnormal growth hormone response to either oral glucose ingestion or thyrotropin-releasing hormone; and (*c*) elevated concentration of basal somatomedin C/insulinlike growth factor I (SmC/IGF I).[1] Four patients had elevated basal growth hormone level (≥10 ng/ml). All but one had elevated SmC/IGF I level (≥1.50 U/ml). Their fasting blood glucose levels were within the normal range, and none of the patients had any clinical or laboratory signs of adrenal, thyroid, or gonadal insufficiency at the time of the investigation. Apart from acromegaly, the patients were otherwise healthy and physically active, and none had taken any drugs known to affect adipose tissue metabolism or insulin secretion. 14 healthy control subjects, matched for sex, age, and body weight, were included for comparison. The clinical data relating to the study groups are given in Table I. The diet of the acromegalic patients and the control subjects consisted of ~45% carbohydrate, 35% fat, and 20% protein, and ~7–8.5 megajoule, according to a 24-h recall.

The patients and the control subjects were investigated in the outpatient department at 8 a.m., after an overnight fast. After a 30–60-min rest, venous blood samples were taken for determinations of the fasting levels of glucose (7), plasma immunoreactive insulin (8), growth hormone (9), and SmC/IGF I (10). Specimens of subcutaneous adipose tissue (~5 g) were then removed surgically from the gluteal region. The biopsy was taken from the left or the right side in a randomized way. Field-block local anesthesia was induced in a way that did not influence the adipose

1. *Abbreviations used in this paper:* ED_{50}, half-maximum effect; K_{itt}, rate constant; SmC/IGF 1, somatomedin C/insulinlike growth factor I.

tissue metabolism (11). Thereafter, 100 g of glucose was given orally and samples of venous blood were drawn at 15, 30, 45, 60, 90, and 120 min for determinations of glucose and insulin. 60 min after the oral glucose load, another smaller fat biopsy (~1.5 g) was taken from the contralateral gluteal region. Insulin binding and lipolysis were investigated in both biopsies, but glucose metabolism only in the first biopsy.

On another day, and after an overnight fast, the in vivo insulin sensitivity was measured by means of an insulin tolerance test; crystalline porcine insulin (0.1 U/kg body weight) was rapidly injected intravenously. After 2.5, 5, 7.5, 10, 15, 20, 25, and 30 min, blood glucose was determined. A rate constant (K_{itt}) was derived from a semi-logarithmic plot of the fall in blood glucose level after the insulin injection. In methodological studies, subcutaneous adipose tissue was obtained during gall-bladder surgery from nonobese otherwise healthy subjects.

The study was approved by the Ethics Committee of the Karolinska Institute. Each subject was given a detailed description of the study and their consent was obtained.

Insulin binding to isolated fat cells. Isolated fat cells (12) were incubated in triplicate for 60 min at 24°C in Krebs-Henseleit bicarbonate buffer (pH 7.4) containing albumin (40 mg/ml), glucose (2 mg/ml), mono-^{125}I-(Tyr A_{14})-insulin (0.05 nmol/liter), and unlabeled insulin (0–50 nmol/liter), as described in detail elsewhere (5). Nonspecific binding was measured in the presence of 20 μmol/liter of unlabeled insulin. All data were corrected for the nonspecific binding, which amounted to 3–4% of the total binding. Insulin degradation was negligible. The results of the binding studies based on fat cell number and fat cell surface area were presented as a plot of the percentage of the specifically bound ^{125}I-insulin vs. the total insulin concentration (competition-inhibition curve). Receptor number and affinity was not determined because of current uncertainties in interprelation of insulin binding data (13). The coefficient of variance for insulin binding was 5%.

Adipose tissue glucose metabolism. In this clinical-experimental study, where only limited amounts of adipose tissue was available, it was desirable to use a method for the determination of glucose utilization that gave an overall estimation of glucose metabolism. Therefore, methods to specifically study glucose transport or radioactive glucose metabolism at tracer substrate concentrations were avoided, since these methods only evaluate the initial transport step in glucose metabolism. Instead, we chose to study the metabolism of radioactive glucose at a physiological substrate concentration where, also, the final steps in glucose breakdown are evaluated (14). In these studies, it was necessary to use segments of adipose tissue instead of isolated fat cells, since we and others have shown that the effect of insulin on glucose metabolism at physiological substrate levels is altered in isolated adipocytes (15, 16). Adipose tissue segments (~100 mg) were incubated in triplicate or quadruplicate for 2 h at 37°C in Krebs-Henseleit bicarbonate buffer (pH 7.4) containing albumin (40 mg/ml), U-[^{14}C]glucose (2×10^6 cpm/ml, 1 mg/ml) and insulin (0–34 nmol/liter). $^{14}CO_2$-production (glucose oxidation) and [^{14}C]glucose incorporation into total lipids (lipogenesis) were determined as described elsewhere (16, 17). In methodological studies it was observed that insulin stimulated $^{14}CO_2$-production in a marked and dose-dependent way. However, the hormone had only a weak and statistically insignificant effect on conversion of radioactive glucose to lipids. Therefore, only $^{14}CO_2$-production was measured in the subsequent studies. The coefficient of variance for glucose metabolism in segments of adipose tissue was 8%. Insulin degradation in the incubation medium was negligible (2–4%).

Determination of fat cell lipolysis. Since lipolysis was measured in two different biopsies from the same subject, it was necessary to use methods to measure the antilipolytic effect of insulin in microsamples of human fat. Such methods have recently been developed in our laboratory using dilute adipocyte suspensions and a bioluminescens lipolysis assay (18, 19). It was possible to use isolated fat cells in this situation, since the collagenase isolation procedure does not alter the effect of insulin on human adipocyte lipolysis (16). Isolated fat cells were incubated at a final concentration of 2% (vol/vol) in Krebs-Henseleit bicarbonate buffer containing glucose (2 mg/ml), albumin (40 mg/ml), isoprenaline (0 or 6×10^{-6} mol/liter), and insulin (0–7 nmol/liter), as described previously (5). Each incubation was run in duplicate for 2 h at 37°C with O_2–CO_2 (95:5) as the gas phase. It was necessary to use a high glucose concentration in the medium in order to obtain a constant antilipolytic effect of insulin in the isoprenaline experiments, since fat cells sometimes were resistant to insulin at glucose concentrations below 2 mg/ml (18). The total incubation volume was 0.2 ml. After incubation, aliquots of the medium were removed for the determination of glycerol (19), which was used as an index of lipolysis. The coefficient of variance for glycerol release was 5%. The rate of lipolysis was linear for at least 3 h.

Fat cell determinations. Fat cell size was measured by the method of Sjöström and co-workers (20). Mean fat cell volume, weight, and surface area were determined from previously derived formulas (21, 22). The lipid weight of the incubated sample was determined gravimetrically, after extraction of lipids with heptane, as described in detail elsewhere (17). The number of fat cells incubated was determined by dividing the lipid weight of the incubated sample by the mean fat cell weight.

Chemicals. Crystalline, glucagon-free porcine insulin was generously supplied by Vitrum AB, Stockholm, Sweden. Mono-^{125}I-(Tyr A_{14})-insulin was obtained from Novo Research Institute, Copenhagen, Denmark, and bovine serum albumin (fraction V) came from the Armour Pharmaceutical Co., Eastbourne, England. U-[^{14}C]glucose (specific activity 268 mCi/mmol) was obtained from the Radiochemical Center, Amersham, England, and collagenase (type I) was purchased from Sigma Chemical Co., St. Louis, MO.

Expression of the results. The amplitude (responsiveness) and the left-right position (sensitivity) of the dose-response curves for insulin-induced stimulation of glucose oxidation and inhibition of lipolysis were evaluated, as described in detail previously (23). The ascending part of the dose-response curves was linearized by log-logit transformation (23) and the concentration of insulin producing the half-maximum effect (ED_{50}) was calculated by linear regression analysis. The obtained log value for insulin concentration was transformed to the corresponding lin value. Insulin responsiveness was defined as the absolute values of glycerol release, or $^{14}CO_2$-production at the maximum effective hormone concentration minus the basal value (i.e., with no insulin present).

Statistical analysis. The reported values are the mean±SEM. The statistical significance of the individual data was determined by the Student's t test, using the paired t test when applicable. Linear regression analysis by the method of least squares was performed (24).

Results

In vivo insulin action. In the fasting state, the acromegalic patients displayed moderate hyperinsulinemia; the insulin level was 2–3 times higher than that in the control group ($P < 0.001$, Table I). After the oral glucose load, the increase in blood glucose and plasma insulin were more pronounced in the acromegalic than in the control subjects (data not shown). The blood glucose and plasma insulin levels at 1 h after the oral glucose challenge were significantly increased in the acromegalic patients as compared with the control subjects (Table I).

The in vivo hypoglycemic response to exogenous insulin, as measured by the insulin tolerance test, was ~40% lower in the acromegalic than in the control subjects ($P < 0.01$, Table I).

Fat cell size. The fat cell size was 20% smaller in the acromegalic patients than in the controls ($P < 0.05$, Table I). In neither group was the fat cell size altered after the oral glucose load (data not shown).

Glucose metabolism in fasting state. Glucose oxidation is shown in Fig. 1. The basal rate of adipose tissue glucose oxidation in the acromegalic patients was significantly reduced—by ~45%—as compared with that in the control group ($P < 0.05$). In the latter group, insulin induced a dose-dependent stimulation of adipose tissue $^{14}CO_2$-production, the ED_{50} value being ~0.55 nmol/liter. In the acromegalic patients, the insulin stimulation of glucose oxidation was markedly reduced; at none of the hor-

Table I. Clinical and Metabolic Characteristics of the Study Groups

Study group	n	Sex (F/M)	Age	Body weight (% of average)	Fasting glucose	Plasma glucose 1 h after oral	Fasting insulin	Plasma insulin 1 h after oral	Fasting hGH	Fasting SmC/IGF I	K_{itt}	Gluteal fat cell volume
			yr		mmol/liter	mmol/liter	mU/liter	mU/liter	ng/ml	U/ml	% min	pl
Control	14	7/7	43±4	104±2	4.7±0.1	5.5±0.3	6.6±1.0	37.5±7.2	8.0±2.9	0.7±0.1	4.7±0.4	996±57
Acromegaly	9	4/5	47±4	106±2	5.0±0.1	7.1±0.3	16.8±2.8	75.6±14.9	28.8±11.8	3.0±0.3	2.7±0.4	812±44
Sign, p, contr vs. pats		NS	NS	NS	NS	<0.05	<0.001	<0.05	<0.01	<0.001	<0.01	<0.05

Plasma insulin and glucose were determined in the fasting state and 1 h after a 100-g oral glucose load. In vivo insulin sensitivity (K_{itt}) was determined as described in Methods. Values are mean±SE. The average body weight was obtained from Documenta Geigy (36). n, number of subjects. The significance of the differences between controls and acromegalics were determined by the Student's t test. p, Level of significance.

mone concentrations tested (0.017–34 nmol/liter) was there a statistically significant effect of insulin.

Insulin binding before and after oral glucose. Insulin binding is shown in Fig. 2. After an overnight fast, the specific adipocyte insulin binding per number of cells at low concentrations of insulin was significantly reduced by 20–30% in the acromegalic patients as compared with the control subjects. Expression of insulin binding per unit of cell surface area tended to reduce the difference between the two groups, due to a smaller mean cell size in the acromegalics. However, the difference was still statistically significant. At higher hormone concentrations, insulin binding was almost identical in the two groups whether it was calculated on the basis of cell number or cell surface area.

After glucose ingestion, the difference in insulin binding between the two groups was further enhanced. Hence, at low concentrations of insulin, the specific insulin receptor binding was ~50% lower in the acromegalic patients than in the controls ($P < 0.01$), whether it was expressed on the basis of fat cell number or per fat cell surface area. At higher insulin concentrations, however, insulin binding was similar in the two groups.

The effects of glucose ingestion on insulin binding in the acromegalic patients and in the control subjects were also evaluated by comparing the results obtained with pre- and postoral glucose adipocytes. In the acromegalic patients, insulin binding at insulin concentrations below 2 nmol/liter was significantly lower after than before oral glucose, the decrease being ~30% ($P < 0.05$). At higher insulin concentrations, the insulin binding was similar in pre- and postglucose adipocytes. In the control subjects, on the other hand, insulin binding at low concentrations of the hormone was significantly increased by 20% ($P < 0.05$) after glucose ingestion, whereas at higher insulin concentrations it was the same as before glucose.

Lipolysis before and after oral glucose. After an overnight fast, basal and isoprenaline-induced rates of lipolysis as well as

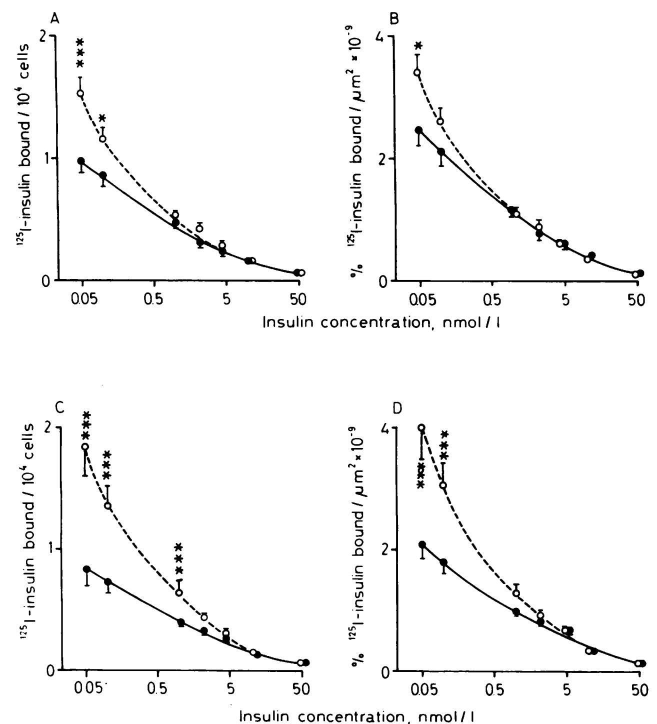

Figure 2. Specific insulin binding to isolated fat cells obtained after an overnight fast before and 60 min after a 100-g oral glucose load in acromegalic patients (•) and control subjects (o). The binding data are presented as competition-inhibition curves. *A* and *B* denote insulin binding before glucose ingestion per fat cell number (*A*) and per cell surface area (*B*). *C* and *D* denote insulin binding after glucose ingestion per cell (*C*) and per cell surface area (*D*). The statistical significance of the differences between the groups was determined with the Student's unpaired *t* test, *$P < 0.05$; ***$P < 0.01$. For further details, see legend to Fig. 1.

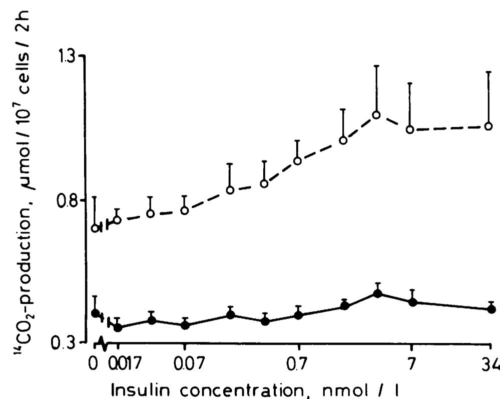

Figure 1. Effect of insulin on adipose tissue glucose oxidation in acromegalic patients (•) and control subjects (o). Subcutaneous adipose tissue was obtained after an overnight fast, and was incubated with U-[^{14}C]glucose in the absence and presence of various insulin concentrations. $^{14}CO_2$-production was determined and used as index of glucose oxidation. Values are mean±SE.

Table II. Basal and Isoprenaline-induced Lipolysis, and Insulin Responsiveness

	Glycerol release				Responsiveness			
	Before glucose		After glucose		Before glucose		After glucose	
Study group	Basal	Isoprenaline	Basal	Isoprenaline	Basal	Isoprenaline	Basal	Isoprenaline
Control	6.4±2.1	31.4±8.3	5.2±1.6	30.3±1.7	3.8±1.7	8.6±1.7	2.7±1.1	9.6±2.5
Acromegaly	5.9±1.0	38.5±7.8	5.9±1.1	36.4±7.7	2.7±0.6	7.6±0.6	2.8±1.5	5.7±1.3

Isolated fat cells were incubated from 11 control subjects and 9 acromegalic patients before and 60 min after a 100-g oral glucose load. The cells were incubated in the basal state or with isoprenaline (6×10^{-6} M), and with insulin (0–7 nmol/liter). Glycerol release (μmol/10 cells/2 h) was determined. Responsiveness equals glycerol release in the absence of insulin, minus glycerol release at the maximum effective insulin concentration. Values are mean±SE.

the antilipolytic effect of insulin were similar in the control subjects and the acromegaly patients. In both groups, the rate of lipolysis was increased 5–6-fold by 6×10^{-6} M of isoprenaline, and insulin responsiveness was ~50% in the basal and 30% in the presence of isoprenaline (Table II). Furthermore, insulin sensitivity was almost identical in the two groups. The mean dose-response curves were almost superimposed both in the basal state (Fig. 3) as well as in the presence of isoprenaline (figure not shown). The individual ED_{50} values were similar in the two groups, 60–80 pmol/liter (Table III).

In fat cells obtained after oral glucose, control subjects and acromegaly patients displayed similar rates of basal and isoprenaline-induced lipolysis as well as insulin responsiveness (Table II). However, the mean dose-response curves for antilipolysis were markedly shifted to the right in acromegaly as compared with the control state. This was true in the basal state (Fig. 3) as well as in the presence of isoprenaline (figure not shown). The individual ED_{50} values were ~60 times higher in acromegaly than in the control state (Table III). Thus, after glucose ingestion, the sensitivity of the antilipolytic effect of insulin was markedly inhibited in acromegaly as compared with the control state.

The effects of glucose ingestion on lipolysis was also evaluated. Oral glucose did not alter basal lipolysis, isoprenaline-induced lipolysis or insulin responsiveness in the two study groups (Table II). When the mean ED_{50} values for insulin inhibition of basal lipolysis were compared (Table III), glucose ingestion induced a threefold increase in hormone sensitivity in control subjects ($P < 0.01$), whereas it induced a twofold decrease in insulin sensitivity in acromegaly ($P < 0.05$). The results with isoprenaline-induced glycerol release were similar to those in the basal state. Thus, in the control group, the insulin sensitivity increased sevenfold after glucose ingestion ($P < 0.01$), and in acromegaly it decreased by a factor of 10 after glucose ($P < 0.05$).

The individual values for ED_{50} were not correlated with the individual values for tracer insulin binding in the two groups (data not shown).

Correlations between insulin action and circulating levels of growth hormone, insulin, and SmC/IGF I. Insulin binding, insulin-induced glucose oxidation, and antilipolysis were similar in the four acromegaly patients with high growth hormone levels, as in the five acromegaly patients with low growth hormone levels. In the control and acromegaly groups, neither the fasting levels of insulin nor SmC/IGF I were correlated with insulin binding. The effects of insulin on lipolysis and glucose oxidation were also not correlated with the circulating levels of insulin or SmC/IGF I in the two groups.

Discussion

The results of previous studies (1–4) indicate that peripheral tissue insulin resistance may be of importance for the diabetogenic effect of acromegaly in man. In the present study, the in vivo action of insulin was markedly reduced in the acromegalic patients, as evidenced by the results of the insulin tolerance test and the oral glucose load. Moreover, the results with adipose tissue in acromegaly show clearly that, in the fasting state, the effect of insulin on glucose utilization is almost completely abol-

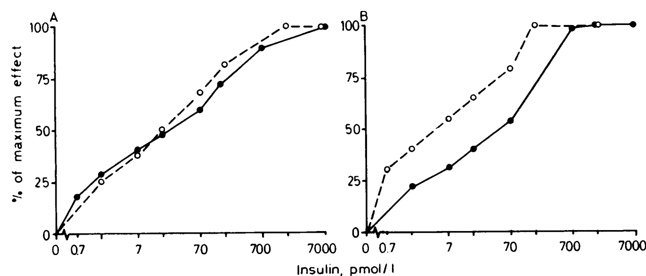

Figure 3. Insulin inhibition of basal glycerol release in isolated fat cells obtained after an overnight fast before (*A*) and 60 min after (*B*) a 100-g oral glucose load in acromegalic patients (●) and control subjects (○). The antilipolytic effect of insulin was calculated as the rate of glycerol release in the absence of insulin minus the rate in the presence of insulin, and is expressed as a percentage of the maximum insulin effect. The mean dose-response curve for each group is shown.

Table III. Sensitivity of the Antilipolytic Effect of Insulin

	ED_{50} (*pmol/liter*)					
	Basal			Isoprenaline		
Study group	Before glucose	After glucose	*P*	Before glucose	After glucose	*P*
Control	65±34	20±13	<0.01	79±38	12±5	<0.01
Acromegaly	57±30	116±39	<0.05	70±19	708±245	<0.05
P	NS	<0.05		NS	<0.05	

The concentration of insulin giving ED_{50} was determined from the individual dose-response curves as described in Methods. Student's paired and unpaired *t* tests were used for statistical comparison of results within and between groups, respectively.

ished and insulin binding is somewhat reduced, whereas the antilipolytic effect of the hormone remains unaffected. Furthermore, after oral glucose ingestion, the resistance to insulin in acromegaly is further enhanced, also involving insulin-induced antilipolysis.

After an overnight fast, insulin binding was 20–30% decreased in the acromegalic patients owing essentially to a decrease at low insulin concentrations, but not to a change at high hormone concentrations. This indicates that the total binding capacity was not altered in acromegaly. These results differ from those previously reported (25, 26), where acromegalic patients showed a decrease in the total binding capacity of insulin. However, in those earlier studies, monocytes were investigated in which insulin has little or no metabolic effect (27). Therefore, these cells may not be representative for insulin target tissues.

The small reduction of insulin binding in acromegaly after an overnight fast that was observed in this study seems not to be of critical importance for the diminished effect of the hormone on adipose tissue glucose utilization. Hence, the effect of insulin on adipose tissue glucose oxidation was almost completely blunted at insulin concentrations of up to 34 nmol/liter, whereas insulin receptor binding was decreased only at insulin concentrations below 1 nmol/liter. Moreover, insulin responsiveness, which is thought to reflect insulin action at steps distal to the hormone-receptor interaction (28, 29), was markedly decreased in the acromegalic patients. Thus, our findings indicate a postbinding defect in insulin-induced adipose tissue glucose oxidation in acromegaly. The antilipolytic effect of insulin was, however, not altered in acromegaly in the fasting state. The latter finding indicates that acromegaly may act selectively on a separate intracellular pathway of insulin action. The finding that the sensitivity of the antilipolytic effect of insulin was normal in the acromegalic patients constitutes further evidence that the small decrease in insulin binding is not of importance for the insulin resistance noted in acromegaly in the fasting state. It is generally known that insulin produces its maximum metabolic effects when only a minute fraction of the total number of receptors is occupied (28, 29). This means that cells possess spare receptors. It is therefore possible that a rather small decrease in insulin binding does not induce a concomitant reduction in insulin sensitivity. This theory is further supported by two recent studies on human fat cells. Taylor and co-workers (30) observed a 30% reduction in insulin binding in hyperthyroid patients as compared with control subjects, but this was not accompanied by an alteration of the adipocyte insulin sensitivity, as judged by ED_{50} values for lipogenesis and glucose transport (30). When we infused glucose intravenously to healthy nonobese subjects, a 30% reduction in tracer insulin binding, but no change in the sensitivity of the antilipolytic effect of insulin, was observed 30–60 min after the start of the intravenous glucose load (31).

In adipocytes obtained from the control subjects 1 h after glucose ingestion, the insulin binding at low hormone concentrations and the sensitivity to the antilipolytic effect of insulin were enhanced, which is in agreement with previous observations (5). However, in the acromegalics, the insulin binding at low hormone concentrations and the sensitivity to insulin-induced antilipolysis were significantly decreased after glucose ingestion. Consequently, the difference in insulin binding between the two groups was further enhanced to ~50%. At the same time, the sensitivity to the antilipolytic effect of insulin was markedly more decreased in the acromegalic patients than in the controls after glucose ingestion. This was true when basal or isoprenaline-induced lipolysis was investigated. These results indicate that in acromegaly, the resistance to insulin is further enhanced after glucose ingestion, involving also the antilipolytic effect of the hormone. Although the mechanisms behind this are unclear, it is not likely that the further small decrease in insulin binding is the sole factor responsible for the marked inhibition of sensitivity of insulin-induced antilipolysis in the postoral glucose adipocytes of the acromegalic patients. It is generally believed that changes in insulin sensitivity reflect alterations in receptor binding (28, 29). However, insulin sensitivity can also be modified by alterations in the coupling between the receptor and effector, which can take place independently of the hormone-binding event. The present data best fit the notion that the coupling between the insulin receptor and antilipolysis is modified by glucose ingestion. If so, oral glucose enhances the coupling, and thereby stimulates the insulin sensitivity, in healthy subjects. In insulin-resistant acromegaly patients, oral glucose inhibits the coupling process, which is followed by a decreased insulin sensitivity. In the latter situation, changes in insulin binding may have no or only small additional effects on insulin sensitivity. Note that there was no correlation between insulin binding and ED_{50} in the present study. This supports further the concept that alterations in coupling rather than in binding are of importance for the findings with insulin sensitivity in acromegaly. At present it is not known whether the insulin-induced stimulation of glucose oxidation is also modified by glucose ingestion. Unfortunately, large amounts of fat are required for such investigations. Therefore, it was not possible to study in vitro glucose metabolism twice in the same subjects.

The factors mediating the insulin resistance in acromegaly are not known. A long-term elevation of the circulating levels of growth hormone may induce a state of insulin resistance (32, 33). Furthermore, long-term exposure of human adipocytes to growth hormone in vitro markedly reduced the basal and insulin-stimulated rates of glucose metabolism (34, 35). However, there is probably no direct effect of the circulating growth hormone level on insulin action on adipose tissue in acromegaly, since we observed similar insulin effects in acromegaly patients with high and low growth hormone levels. The hyperinsulinemia associated with acromegaly is probably not important for the inhibited insulin action. First, the insulin levels were neither correlated with the insulin binding capacity nor with the insulin responsiveness in adipose tissue. Second, in another report (23) we observed no effect of hyperinsulinemia on insulin action in human adipose tissue.

In conclusion, the present study demonstrates that, in acromegalic patients with in vivo insulin-glucose resistance, the action of insulin on glucose utilization by adipose tissue is markedly deteriorated in the fasting state, mainly owing to alterations at the postbinding level. After glucose ingestion, the resistance to insulin is further enhanced in acromegaly, involving also the antilipolytic effect of the hormone. An inhibition of the coupling between the insulin receptor and effector alone or in combination with a further decrease in insulin binding may explain the increase in insulin resistance after glucose ingestion. These mechanisms may be important factors for the diabetogenic effect of acromegaly in man.

Acknowledgments

We are indebted to Linda Fryklund and Anna Skottner, Kabi Vitrum AB, Stockholm, Sweden, for their generous help with measurements of plasma SmC/IGF I.

This study was supported by grants from the Swedish Medical Research Council (Project 1034), the Karolinska Institute, the Swedish Medical Association, the Nordic Foundation, the Swedish Diabetes Association, and the Groschinsky, Wiberg, Tore Nilson, Osterman and Folksam Research Foundations.

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