Corticosteroid receptors in mononuclear leucocytes of obese subjects

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Abstract

Abnormalities of the hypothalamus–pituitary–adrenal axis and hypersensitivity to corticosteroids have been suggested as major determinants of the development of visceral obesity. Since at the cellular level most effects of corticosteroids are mediated by specific receptors, we evaluated the number of type I and type II corticosteroid receptors in mononuclear leucocytes of 26 obese and 13 control subjects. We also studied the relationship between corticosteroid receptors, measured by radioreceptor assay, and abdominal visceral fat, evaluated by computed tomography scan, plasma and urine corticosteroid hormone concentrations and overall glucose metabolism, assessed by euglycaemic–hyperinsulinaemic clamp.

We observed a decrease in type II receptors in the obese subjects (1746 ± 160 vs 2829 ± 201 per cell; $P<0.0001$), with no change in type I receptors. Type II receptors decreased in relation to body mass index ($r= -0.53$; $P<0.005$) and total glucose disposal ($r=0.51$; $P<0.01$).

Abdominal visceral fat did not correlate with type II receptor number, but did correlate with total glucose disposal ($r= -0.35$; $P<0.05$); the rate of glucose disposal was lower in obese subjects (3.3 ± 0.3 vs 7.4 ± 0.4 mg/kg per min; $P<0.001$). Plasma and urine cortisol did not differ between the two groups. However, a direct correlation between type II receptor number and both plasma ($r=0.43$; $P<0.02$) and urine cortisol concentrations ($r=0.60$; $P<0.05$) was observed.

In conclusion, the number of type II corticosteroid receptors in mononuclear leucocytes was found to be lower in obese subjects. This abnormality appears to be related to the degree of adiposity and to the main endocrine-metabolic features of the obesity syndrome, further supporting the hypothesis of involvement of hypothalamus–pituitary–adrenal axis hyperactivity in the pathophysiology of obesity.

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Introduction

It has been suggested that obesity syndrome in animals has a neuroendocrine aetiology which is responsible for the development of hyperinsulinaemia, increased fat depot and insulin resistance (Bray & York 1979, Jeanrenaud 1994). Several studies of obese animals have demonstrated hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis (Bestetti *et al.* 1990) or glucocorticoid action in the central nervous system (CNS) (Bray & York 1979). It has been reported that the glucocorticoid receptor number is decreased in liver and brain of *ob/ob*, *mdb/mdb* mice and in *fa/fa* rats, and this is probably due to the elevated circulating corticosteroid levels (Webb *et al.* 1986, Shargill *et al.* 1987, Tsai & Romsos 1991). Furthermore, it has been suggested that impaired glucocorticoid receptor function and dysregulation of the HPA axis in transgenic mice may predispose to obesity (Pepin *et al.* 1992).

It has been suggested that in man also, as a consequence of genetic or environmental changes, a primary alteration at the CNS level with subsequent dysregulation of the HPA axis could be a trigger for the development of obesity, increased visceral fat deposition, insulin resistance and arterial hypertension (Bjorntorp 1996). In fact, hyperactivity of the HPA axis with increased adrenocorticotrophin (ACTH) response to stress has been found in obese humans (Pasquali *et al.* 1993, 1996, Weaver *et al.* 1993). The activity of the HPA axis and glucocorticoid action are regulated by binding of corticosteroids to their specific receptors. Quantitative and functional abnormalities of the corticosteroid receptor gene and/or its product have also been suggested to be the cause of human obesity, but so far few studies have been carried out. In fact, data obtained on the glucocorticoid receptor gene have been contradictory: Weaver *et al.* (1992) postulated that in obese patients a polymorphism of the glucocorticoid receptor gene locus was associated with hyperinsulinaemia and insulin resistance, while Clement *et al.* (1996) suggested that the glucocorticoid receptor gene does not play any relevant role in the pathogenesis of morbid obesity.

In obese subjects glucocorticoid receptor density appears to be higher in visceral than subcutaneous adipose tissue, indicating regional variation in glucorticoid receptor distribution. However, few data are available on the characteristics of these receptors in other tissues, in particular at the CNS level. It is clear that a study of the mechanism of action of glucocorticoids in the human brain is not feasible and only indirect methods can be used. In humans the regulation of corticosteroid receptors has been studied extensively in mononuclear leucocytes (MNLs).

There are two types of corticosteroid receptor: type I or mineralcorticoid receptor and type II or glucocorticoid receptor (Funder 1992). It is known that receptor structure does not vary among target tissues, and the preferential binding of cortisol and aldosterone to type I receptors is related to the presence of 11-hydroxysteroid dehydrogenase. However, even if the receptor is the same, the mechanism of action may be different in the different tissues (Bamberger *et al.* 1996).

Studies on adrenalectomized rats have shown that regulation of type I and type II corticosteroid receptors in hippocampus and lymphoid tissue is similar. The hippocampus in rats is involved in the regulation of the corticotrophin-releasing factor (CRF)–ACTH axis, and thus the study of corticosteroid receptors in human MNLs can be considered an index of glucocorticoid receptor regulation at the CNS level (Lowy 1990, 1991).

Previous studies have shown that type II receptors are depressed by administration of exogenous glucocorticoids (Schlechte *et al.* 1982), but in Cushing's syndrome their number is normal and still down-regulated by cortisol (Pardes *et al.* 1989).

Obese subjects show some features similar to those typical of patients with Cushing's syndrome, such as hyperinsulinaemia, insulin resistance and, in some subjects, a predominant visceral localization of fat. Therefore the aim of the present study was to evaluate the number and affinity of type I and type II glucocorticoid receptors in MNLs of obese and control subjects and to examine possible correlations between these parameters and plasma and urine corticosteroid hormone concentrations, and also their relation to fat distribution and insulin sensitivity.

Materials and Methods

Subjects

Twenty-six obese subjects (seven men and nineteen women; age 40 ± 2 years; body mass index (BMI) 39 ± 6 kg/m^2) were selected to enter the study. The presence of other relevant metabolic or endocrine abnormalities was excluded on the basis of clinical history, physical examination and blood tests for routine biochemistry and basal hormone determination. All subjects were submitted to an oral glucose tolerance test to select only those with normal glucose tolerance, evaluated by the criteria of the National Diabetes Data Group (1979). None had high arterial blood pressure.

A group of 13 healthy normal-weight subjects (4 men and 9 women; age 36 ± 2 years; BMI 23 ± 3 kg/m^2) was also included in the study as a control.

All obese and control subjects gave their written informed consent to the study, and the protocol was approved by an internal ethical committee. The subjects of the control group were submitted to the same experimental procedure as those of the obese group, except for the computed tomography scan, which was avoided for ethical reasons.

No subject was dieting or taking medication in the month before the study. All were instructed to consume a weight-maintaining diet with at least 250–300 g carbohydrates a day over the 3 days before the study.

Anthropometrical characteristics

Body composition was determined by bioelectric impedance (BIA 101 impedance analyser; RJL System, Detroit, MI, USA), determining body fat, fat-free mass and total body water by the total conductive volume of the body for each individual.

Waist (minimum values between the iliac crest and the lateral costal margin) and hip (maximum value over the buttocks) circumferences were measured to obtain information on the pattern of body fat distribution. Subcutaneous and visceral adipose tissue in the abdominal region were measured by computed tomography scan, as described by Sjostrom *et al.* (1985), in a single scan at the L4 level. The anthropometric characteristics of the subjects included in the study are reported in Table 1.

Clamp study

All tests were performed in the morning (0830 h), after a 12 h overnight fast, after approximately 30 min of rest with subjects in the supine position. A Teflon catheter was inserted into an antecubital vein for glucose and insulin infusion. A second catheter was inserted retrogradely in a vein of the contralateral hand, which was maintained in a hot box (70 °C) to arterialize venous blood samples. Plasma glucose was determined under basal conditions and every 5 min during the test. After the baseline glucose concentration had been established, a 5 min priming insulin infusion (Actrapid HM; Novo Industries, Mainz, Germany) was followed by a constant infusion of 40 mU/m^2 body surface area per minute for the whole study. To maintain the subjects at their own basal arterial plasma glucose concentration, a 20% glucose solution was infused, modifying the infusion rate on the basis of 5 min glycaemia determinations (De Fronzo *et al.* 1979). The rate of insulin infusion was chosen to suppress hepatic glucose production (HGP) in both control and obese subjects without impaired glucose tolerance (Bonora *et al.* 1992).

Table 1 Characteristics, expressed as mean ± S.E.M., of the obese and control subjects participating in the study

	n	M/F	Age (years)	BMI (kg/m^2)	Waist:hip ratio	Total body water		Fat mass		Fat-free mass	
						Litres	%	kg	%	kg	%
Control	13	4/9	36 ± 2	23 ± 3	0·78 ± 0·04	38·5 ± 2·0	57·9 ± 1·5	14·0 ± 1·2	21·4 ± 1·8	52·2 ± 2·7	78·5 ± 1·8
Obese	26	7/19	40 ± 2	39 ± 6*	0·98 ± 0·16*	48·1 ± 1·4*	45·3 ± 1·3*	36·6 ± 2·1*	33·8 ± 1·6*	70·3 ± 2·0*	66·1 ± 1·6*

*$P<0.0001$ compared with controls.

To confirm this assumption we measured HGP in a few of the subjects (six control and five obese) during the clamp study using D-[3-^{3}H]glucose (Amersham Life Sciences, Amersham, Bucks, UK) as tracer. Starting 180 min before the insulin infusion, the subjects received a primed (25 µCi) infusion (0·25 µCi/min) of D-[3-^{3}H]glucose, which stayed the same until the end of the study.

Blood samples for measurement of D-[3-^{3}H]glucose specific activity were drawn at −30, −20, −10, 0 and during the last 60 min of the clamp every 10 min. Overall glucose disposal was estimated from the D-[3-^{3}H]glucose specific activity, using Steele's (1959) non-steady-state equations.

Taking into account the fact that changes in specific activity could be dependent on changes in exogenous unlabelled glucose infusion rate (GIR) and on unlabelled HGP, the total unlabelled glucose appearance in the blood compartment is R_a (mg/min)=GIR+HGP; and then HGP=R_a − GIR.

In our experimental conditions HGP was completely suppressed in both normal and obese subjects, therefore GIR (mg/kg per min) can be used as a measure of total body glucose disposal (M). The duration of the clamp was approximately 120 min in each individual. Plasma insulin concentrations at the end of the clamp rose to approximately 100 µU/ml in both obese and normal-weight subjects.

Between −30 and 0 min and during the last 30 min of the clamp, rates of O_2 consumption and CO_2 production were measured by continuous indirect calorimetry in a ventilated hood (MMC HORIZON System Sensor Medics, Anaheim, CA, USA). O_2 consumption and CO_2 production were used to compute glucose oxidation using Vernet's formula (Vernet *et al.* 1986).

Hormones and biochemistry

Plasma glucose concentrations were measured immediately by the glucose oxidase method (Beckman Glucose Analyser II, Beckman Institute, Fullerton, CA, USA). Plasma non-esterified fatty acids (NEFAs) were assayed enzymically using the NEFA Quick 'BMY' kit (Boehringer Mannheim Yamanouki KK, Tokyo, Japan). Insulin, cortisol and aldosterone were determined by RIA using commercial kits (Insik-5 Sorin, Saluggia, Italy;

Cortisolo Diagnostic System Laboratories, Webster, TX, USA; Aldosterone Radim, Pomezia-Roma, Italy).

Corticosteroid receptors assay

Corticosteroid receptors were measured by a radioreceptor assay, as previously described in detail (Armanini *et al.* 1985*a*, *b*). Briefly, a 50 ml heparinized blood sample was collected at 0800 h while the patients were in a sitting position. MNLs were separated by Percoll gradient and an aliquot was incubated with increasing amounts of [^{3}H]aldosterone (specific activity 84 Ci/mmol) (type I) or [^{3}H]dexamethasone (specific activity 39 Ci/mmol) (type II). Incubation was performed with tracer alone or with the addition of an excess of unlabelled competitor (aldosterone or dexamethasone). In the type I assay an excess of a pure glucocorticoid (RU 26988) was added to confine the binding of [^{3}H]aldosterone to type I receptor.

After 1 h of incubation the cells were washed, and radioactivity counted. The binding parameters (affinity and number of receptors) were calculated by Scatchard analysis.

Statistics

All results are reported as the mean ± S.E.M. Comparisons between obese and control subjects were made by one-way between-groups ANOVA (Statistica for Windows, Release 5·0, Statsoft Inc. 1993, Tulsa, OK, USA). Linear regression analysis was performed by standard techniques.

Results

Table 1 shows the anthropometric characteristics of the subjects. The massively obese subjects exhibited predominantly abdominal fat distribution, as demonstrated by the waist:hip ratio; there were no significant differences between sexes. Characterization of the abdominal adipose tissue in the obese subjects, evaluated by computed tomography scan, showed a visceral area of 206 ± 102 cm^2 and a subcutaneous area of 486 ± 138 cm^2 with a visceral:subcutaneous ratio of 0·50 ± 0·05.

Fat-free mass, fat mass and total body water, evaluated by bioelectric impedance, were significantly increased in obese compared with control subjects (Table 1).

Table 2 Metabolic characteristics and values of plasma cortisol, aldosterone and urinary free cortisol of the subjects. Data are means ± S.E.M., $n=13$ for controls and 26 for obese

	Fasting plasma glucose (mmol/l)	Fasting plasma NEFA (µmol/l)	Fasting plasma insulin (pmol/l)	Plasma cortisol (0800 h) (nmol/l)	Plasma aldosterone (nmol/l)	Urinary free cortisol (nmol/24 h)
Control	5·4 ± 0·2	585 ± 61	50 ± 3	417 ± 27	0·55 ± 0·08	178 ± 21
Obese	5·8 ± 0·2	631 ± 36	108 ± 9*	381 ± 34	0·64 ± 0·10	139 ± 15

*$P<0·001$ compared with controls.

Table 3 Results of euglycaemic-hyperinsulinaemic clamp associated with [³H]glucose tracer. Data are means ± S.E.M. for the number of subjects indicated in parentheses

	Total glucose disposal (M) (mg/kg per min)	HGP (mg/kg per min)		Rate of disappearance (mg/kg per min)		Glucose oxidation (mg/kg per min)		Non-oxidative glucose disposal (mg/kg per min)	
		Basal	Clamp	Basal	Clamp	Basal	Clamp	Basal	Clamp
Control	7·4 ± 0·4 (13)	2·8 ± 0·5 (6)	− 0·2 ± 0·4† (6)	2·8 ± 0·5 (6)	7·4 ± 1·6† (6)	1·1 ± 0·1 (6)	2·3 ± 0·4† (6)	1·8 ± 0·2 (6)	4·8 ± 0·4† (6)
Obese	3·3 ± 0·3** (26)	1·4 ± 0·2 (5)	− 0·9 ± 0·2† (5)	1·4 ± 0·2 (5)	1·9 ± 0·2†** (5)	0·8 ± 0·2 (5)	0·9 ± 0·2* (5)	1·8 ± 0·5 (5)	2·2 ± 0·3** (5)

*$P<0·05$, **$P<0·001$ compared with controls; †$P<0·05$ or minus compared with basal.

Table 4 Significant correlations between type II corticosteroid receptor (type II R) and BMI, plasma insulin, total glucose M, plasma and 24 h urinary free cortisol and type I corticosteroid receptors (type I R) in all cases studied ($n=39$)

	M vs BMI	Type II R vs BMI	Type II R vs plasma insulin	Type II R vs M	Type II R vs plasma cortisol	Type II R vs 24 h urinary free cortisol	Type II R vs Type I R
r	− 0·76	− 0·53	− 0·50	0·51	0·43	0·60	0·52
$P<$	0·0001	0·005	0·05	0·01	0·02	0·05	0·005

Fasting insulin was significantly higher in obese than in control subjects ($P<0·001$) (Table 2), and the M value during the clamp study was significantly lower in the former than in the latter ($P<0·001$) (Table 3).

In our subjects a direct correlation between BMI and basal insulin levels and an inverse correlation between M value and fasting insulinaemia were observed (Table 4). There was also a highly significant correlation between M value and BMI (Table 4) and between M value and visceral adipose tissue ($r= − 0·35$; $P<0·05$).

Fasting NEFA levels were 631 ± 36 µmol/l in obese and 585 ± 61 µmol/l in control subjects. They decreased during clamp in both groups, but remained higher in obese subjects (85 ± 17 vs 31 ± 8 µmol/l; $P<0·05$). In the postabsorptive state, the rates of glucose oxidation and non-oxidative glucose disposal were similar in obese and control subjects (Table 3). During the insulin clamp, these rates increased significantly in normal–weight subjects, but no significant variation was observed in obese subjects.

Basal HGP was not statistically different in obese compared with control subjects and was completely suppressed in both groups during hyperinsulinaemic–euglycaemic clamp.

Plasma and 24 h urinary free cortisol levels were not significantly different between the two groups (Table 2).

Figure 1 illustrates type I and type II receptors in obese and control subjects. In the obese group we observed a significant decrease in type II receptors (1746 ± 160 vs 2829 ± 201 per cell; $P<0·0001$), although their affinity was equivalent across the two groups of subjects (11 ± 1 vs 11 ± 1 nmol/l). No significant difference was found in type I receptors between the two groups (obese vs control: 204 ± 30 vs 272 ± 21 per cell).

Taking the results of the two groups of subjects together, we found an inverse correlation between BMI and the number of type II receptors and a direct correlation between the latter and the rate of total glucose disposal (Table 4), while in the obese group the amount of visceral adipose tissue did not correlate with the number of type II receptors ($r=0·21$; $P=0·37$). A positive correlation was found between the number of type II and type I receptors; furthermore we observed a direct correlation
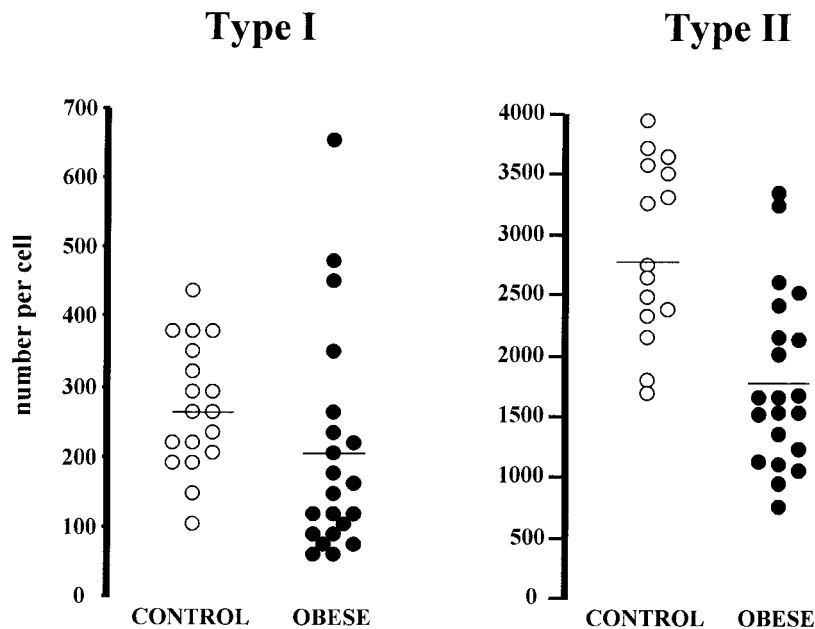
Figure 1 Type I and type II corticosteroid receptors in control and obese subjects. A significant difference (*P*<0·0001) in type II corticosteroid receptors was observed between the control and obese subjects (ANOVA).

between the number of type II receptors and plasma cortisol levels as well as between the number of type II receptors and 24 h urinary free cortisol concentration (Table 4).

Discussion

A very controversial issue in endocrinology is the correlation between changes in steroid receptor number and the extent of biological response (Bamberger *et al*. 1996).

We have previously found a difference in the regulation of type I and type II receptors *in vivo*: type I receptors are down-regulated by an increase in plasma aldosterone or plasma cortisol, as is found in Conn's and Cushing's syndrome, while type II receptors are not decreased by a chronic excess of endogenous glucocorticoids, as is found in Cushing's syndrome (Armanini *et al*. 1993). However, type II receptors are depressed by administration of exogenous glucocorticoids (Hampl *et al*. 1994). We have also observed that, in the normal range, the number of type I and type II receptors significantly correlate with plasma cortisol concentration (Armanini 1994), as confirmed in our present study.

The main findings in the present study were the reduction in type II and the normality of type I corticosteroid receptor number in MNLs from obese insulin-resistant subjects in the presence of normal cortisol concentrations.

In the CNS, type I receptors appear to be more important in the feedback regulation of the CRF–ACTH–cortisol axis, and, in addition, they are also responsible for the immediate response to glucorticoids, as demonstrated by their involvement in the response to dexamethasone administration (Armanini 1994). Type II receptors are bound by cortisol when plasma corticosteroid concentrations are high, e.g. early in the morning or during stress. Therefore our data may be consistent with normal regulation of the HPA axis by variation in corticosteroid concentration in the presence of hypersensitivity of the type II corticosteroid receptor. We did not measure glucocorticoid sensitivity, but indirect evidence may support our hypothesis. In fact, a direct correlation between the number of type II receptors and both plasma and urinary free cortisol was found in the obese subjects, similar to that observed in normal controls, where the up-regulation is associated with a normal number of receptors. An explanation for this phenomenon may be that, in obese subjects, the number of type II receptors in MNLs is set to a lower level genetically to maintain a normal concentration of plasma cortisol. This equilibrium may be primarily associated with hypersensitivity of the type II receptors to cortisol with a subsequently more effective mechanism. Since the affinity of dexamethasone for type II receptors is normal, it is possible that the abnormalities of receptor regulation in our patients are linked to post-receptor mechanisms. Hypersensitivity to hormonal effects has been demonstrated in other

diseases related to corticosteroids, e.g. the pathogenesis of idiopathic hyperaldosteronism is associated with hyper-sensitivity to angiotensin II.

In genetically obese animals, hypersensitivity to corti-costerone has also been suggested (Tokuyama & Himms-Hagen 1987). It has been reported that, in genetically obese mice and rats, liver and brain cytosolic gluco-corticoid receptors decrease with age and body weight, suggesting that the low number of receptors is secondary to the increased circulating corticosterone (Webb *et al.* 1986, Shargill *et al.* 1987, Tsai & Romsos 1991).

Several studies suggest that, in visceral obesity at least, hyperactivity of the HPA axis may exist (Marin *et al.* 1992, Pasquali *et al.* 1993, 1996); furthermore reduced dexa-methasone inhibition of cortisol secretion has been re-ported, suggesting impairment of the glucocorticoid receptors in the CNS. We found a reduction in the number of MNL glucocorticoid receptors, suggesting that this may be an index of increased function. In contrast, a high density of glucocorticoid receptors at the level of adipose tissue has been described in obese subjects (Rebuffè-Scrive *et al.* 1985, 1990, Bjorntorp 1996). Therefore we can speculate that regulation of type II receptors differs in different regions: the density of corti-costeroid receptors seems to be higher in visceral adipose tissue than in other areas of adipose tissue, while in MNLs the number of receptors is reduced in response to a more effective mechanism.

A similar discrepancy in steroid receptor regulation was found in patients with idiopathic hirsutism, who exhibit an increased number of androgen receptors in the skin and a decrease in MNLs in the presence of normal concen-trations of plasma testosterone (Bonne *et al.* 1977, Kuhnle *et al.* 1994, Moghetti *et al.* 1995).

In our experiments we did not observe any difference in either plasma or urinary free cortisol between obese and normal-weight people. This does not exclude the possi-bility that a relative hypercorticism could be present, which would explain some of the metabolic alterations observed in our patients. Evidence has accumulated that both secretion and metabolic clearance rate are increased, thus explaining the common findings of normal or slightly elevated plasma cortisol levels in obese people (Rebuffè-Scrive *et al.* 1990).

In our obese patients the reduction of type II receptors in MNLs associated with normal cortisol concentration prompted us to consider the existence of a more effective mechanism of action of cortisol in obesity. The pathogenic mechanism may be differential genetic hypersensitivity to glucocorticoids in the various target tissues, leading to increased fat in the visceral region, enhanced basal and stimulated insulin secretion and insulin resistance. Gluco-corticoid hypersensitivity of peripheral lymphocytes may be associated with disturbed immunological function, but even though in our study we did not measure any functional aspects of glucocorticoid–MNL interaction, no

data are available on possible impairment of cell-mediated immune response in obesity. Moreover we have recently found that the number of lymphocyte subsets is normal in Cushing's syndrome, in which cortisol plasma levels are clearly elevated (data not shown).

Another mechanism for modulation of glucocorticoid action may be alternative splicing of the glucocorticoid receptor. Evidence is accumulating for alternative splicing being an important determinant of glucocorticoid-receptor-induced gene transcription. Glucocorticoid re-ceptor β lacks the ligand-binding domain and has a dominant negative effect on glucocorticoid receptor α action (Bamberger *et al.* 1996, Guido *et al.* 1996).

It has been recognized for a long time that glucocorti-coids impair insulin-mediated glucose transport and phos-phorylation and inhibit intracellular oxidative glucose metabolism. Moreover treatment with glucocorticoids in-creases the rate of lipolysis, enhancing the oxidative flux of NEFAs to the muscle, which interferes with glucose utilization and oxidation (Rizza *et al.* 1982, Guillaume-Gentil *et al.* 1993, Tappy *et al.* 1994). Chronic gluco-corticoid administration and endogenous hypersecretion both cause elevation of fasting and stimulated insulin levels. This appears to be secondary to insulin resistance. However, since the β-cell is the only cell of Langerhans's islets that contains glucocorticoid receptors (Fischer *et al.* 1990), the changes in insulin secretion may derive from a direct effect of glucocorticoids on the β-cell.

We admitted to the study only obese subjects without overt diabetes or impaired glucose tolerance to avoid any possible effects of hyperglycaemia on the HPA axis. All patients displayed the typical features of obesity syndrome: high plasma NEFA levels, hyperinsulinaemia, reduced insulin-mediated glucose disposal, involving both oxidat-ive and non-oxidative insulin-mediated glucose metab-olism. On the other hand, no change in basal and insulin-mediated suppression of HGP was seen, meaning that the liver exhibited normal insulin sensitivity and that the reduction in the activity of insulin was located only at the periphery. In our population we observed reduced insulin sensitivity and high plasma insulin levels, related not only to the adiposity index, but also to the amount of visceral fat. Moreover the lower the number of type II corticosteroid receptors, the higher the degree of adiposity. In our study an inverse correlation was found between the number of type II corticosteroid receptors and both baseline insulin level and peripheral insulin sensitivity. These observations further support the hypothesis that glucocorticoid hyperactivity may be linked to the β-cell and metabolic abnormalities in obesity. In fact, several studies have shown that the hyperactivity of the HPA axis specifically determines the enlargement of the adipose tissue inside the abdomen (Bjorntorp 1996) and that a predominantly abdominal visceral distribution of fat can increase insulin secretion and reduce insulin sensitivity in obese men (Lillioja *et al.* 1987) and women (De Fronzo

et al. 1979, Macor *et al.* 1997). This seems to be in contrast with our study, in which the number of type II glucocorticoid receptors appeared to correlate indirectly with the degree of obesity, but not with the amount of visceral fat. However, it is interesting to note that, in a study examining the glucocorticoid receptor gene locus as a candidate gene for human obesity, no association was found between obesity and fat distribution, but a strong positive association between the polymorphism of the candidate gene locus and hyperinsulinaemia and insulin resistance was noted in obese patients (Weaver *et al.* 1992).

In conclusion, type II corticosteroid receptor number, evaluated in MNLs, is decreased in obese people. This abnormality appears to be linked to the degree of adiposity and the main endocrine-metabolic features of obesity syndrome.

Acknowledgements

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