

Muscle Sympathetic Nerve Activity in Patients with Acromegaly

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ABSTRACT

Muscle sympathetic nerve activity was measured in nine acromegalic patients (age, 35 ± 4 yr; body mass index, 28 ± 2 kg/m²) and eight healthy subjects (age, 32 ± 3 yr; body mass index, 25 ± 2 kg/m²) by combining the forearm arterial-venous difference technique with the tracer method [infusion of tritiated norepinephrine (NE)]. Muscle NE release was quantified both at rest and during physiological hyperinsulinemia while maintaining euglycemia (~ 90 mg/dL) by means of the euglycemic clamp.

Arterial plasma NE was similar in the two groups at rest (197 ± 28 and 200 ± 27 pg/mL⁻¹) and slightly increased during insulin infusion. Forearm NE release was 2.33 ± 0.55 ng-liter⁻¹·min⁻¹ in healthy subjects and 2.67 ± 0.61 ng-liter⁻¹·min⁻¹ in acromegalic subjects in the basal state and increased to a similar extent during

insulin infusion in both groups (3.13 ± 0.71 and 3.32 ± 0.75 ng·L⁻¹·min⁻¹, $P < 0.05$ vs. basal), indicating a normal stimulatory effect of insulin on muscle sympathetic activity. In contrast, insulin-stimulated forearm glucose uptake was markedly lower in acromegalic patients (2.3 ± 0.4 mg·L⁻¹·min⁻¹) than in control subjects (7.9 ± 1.3 mg·L⁻¹·min⁻¹, $P < 0.001$), indicating the presence of severe insulin resistance involving glucose metabolism.

Our data demonstrate that patients with long-term acromegaly have normal sympathetic activity in the skeletal muscle in the basal, postabsorptive state and normal increments in NE spillover in response to the sympatho-excitatory effect of insulin. Thus, the presence of severe insulin resistance in acromegaly is not accounted for by adrenergic mechanisms. (*J Clin Endocrinol Metab* 85: 3203–3207, 2000)

THE ELEVATED GH levels in patients with acromegaly strongly affect nutrient metabolism and contribute to premature mortality for cardiovascular disease (1, 2). The metabolic abnormalities include hyperlipidemia (3), insulin resistance with compensatory hyperinsulinemia (4–6), and in the long term may lead to overt diabetes. Chronic GH hypersecretion is also associated with cardiovascular changes, encompassing myocardial hypertrophy, increased heart rate and cardiac output, and decreased systemic vascular resistance, all of which contribute to the so-called hyperkinetic heart syndrome (7, 8). If acromegaly is untreated or treated unsuccessfully, the clinical picture may progress toward cardiac dysfunction and, eventually, congestive heart failure (8). Arterial hypertension, frequently observed in acromegalic patients, is a major determinant of the deterioration of cardiac function (8). Whether the metabolic and cardiovascular abnormalities present in acromegaly are entirely accounted for by GH hypersecretion itself or are at least, in part, mediated by other factors is still uncertain.

Catecholamines may be a plausible candidate because sympathetic overactivity causes insulin resistance (9, 10), raises arterial blood pressure (11), and increases cardiovascular mortality (12). Thus, a heightened sympathetic drive could provide a pathogenetic basis for most of the clinical features of acromegaly. To date, few studies have addressed this issue. Some authors reported increased basal levels of

norepinephrine (NE) (13, 14), whereas others were unable to confirm this finding (15, 16). A more recent study showed the lack of circadian rhythm in catecholamine levels in active acromegaly, which was restored after surgical correction (17).

In the above studies, sympathetic nervous system (SNS) activity was evaluated by measuring plasma catecholamine levels. However, plasma NE is a poor index of sympathetic tone because the NE level is determined not only by the rate of its release but also by the rate at which it is removed from the circulation. In addition, sympathetic activation is not uniformly distributed in the body (*i.e.* in some districts the SNS drive may be increased while, at the same time, it is normal or even reduced in others) (18). Hence, the need to adopt methodological approaches that allow estimation of regional rather than global SNS activity.

The aim of the present study was to evaluate in patients with acromegaly the sympathetic outflow in the skeletal muscle, a site of key importance from both a metabolic and a hemodynamic standpoint. To adequately explore this issue, we combined the forearm perfusion technique with the infusion of tritiated NE to measure NE release from the skeletal muscle both in the basal state and during hyperinsulinemia, which acts as a physiological sympatho-excitatory stimulus.

Subjects and Methods

Subjects

The study group consisted of eight normal subjects [age, 32 ± 3 yr; body mass index (BMI), 25 ± 2 kg/m²] and nine patients with untreated active acromegaly (age, 35 ± 4 yr; BMI, 28 ± 2 kg/m²). The relevant characteristics of the subjects are given in Table 1. Diagnosis of acro-

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megaly was based on elevated GH levels not suppressible below 2 $\mu\text{g/L}$ by oral glucose test, high insulin-like growth factor 1 (IGF-I) levels for age, signs and symptoms of the disease, and radiological evidence of pituitary adenoma. The approximate duration of the disease was 9 ± 2 yr, estimated by the clinical history and by comparison with old photographs of the patients. Thyroid, adrenal, and gonadal functions were normal. Only one patient had mild hypertension according to the World Health Organization criteria. None of the subjects was taking any medication. Written informed consent was obtained from all participants. The experimental protocol was approved by the Ethics Committee of the University Federico II of Naples. The use of tracers for research purpose in human subjects was approved by the National Health Authority.

Procedures

All subjects were studied in the postabsorptive state in the supine position after a 12–14-h overnight fast. The forearm perfusion technique (19) was performed as described previously (9). A plastic cannula was introduced in a retrograde manner into a large antecubital vein and threaded as deeply as possible for sampling of blood flowing primarily from muscle tissue. A second cannula was inserted into the ipsilateral brachial artery. This was used for infusion of indocyanine green dye (Cardio-Green; Hynson, Westcott and Dunning, Baltimore, MD) to measure forearm blood flow as well as to sample arterial blood. A contralateral arm vein was also cannulated for the infusion of test substances. During blood collection, a sphygmomanometer cuff placed around the wrist was inflated 100 mm Hg above the systolic arterial pressure to exclude the hand from the circulation. Soon after blood collection, indocyanine green dye was infused through the arterial catheter while keeping the cuff inflated around the wrist. After 4–5 min, two consecutive blood samples were taken to measure the plasma concentration of the dye.

After complete instrumentation, the subjects received iv a priming dose (27 μCi) of L-(2,5,6- ^3H) NE (New England Nuclear, Boston, MA), followed by a continuous infusion at the rate of 0.63 $\mu\text{Ci}/\text{min}$ throughout the experimental period. The NE infusate was prepared with 0.9% saline with the addition of ascorbic acid to prevent oxidation. After a 40-min equilibration period, two consecutive pairs of blood samples were taken simultaneously from the arterial and venous catheters for unlabeled and tritiated NE, serum insulin, and plasma glucose determinations. Then, an infusion of regular insulin was started through the peripheral vein at a rate of 1 $\text{mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 120 min to raise peripheral insulin concentration to postprandial levels. To maintain plasma glucose at its basal value, a variable amount of glucose was also infused. The glucose infusion rate was adjusted by measuring arterial plasma glucose at 5–10-min intervals by means of a glucose analyzer (Beckman Instruments, Fullerton, CA). Arterial and venous blood sampling and blood flow measurements were performed at 90 and 120 min during insulin infusion.

Analytical methods

Plasma glucose was determined on a Beckman glucose analyzer and converted to blood glucose according to hematocrit. Serum insulin was measured by RIA. Serum GH was measured by immunoradiometric

assay (HGH-CTK-IRMA; Sorin, Saluggia, Italy). The sensitivity of the assay was 0.6 mU/L (1 $\mu\text{g/L}$ corresponds to 3 mU/L). The intra- and interassay coefficients of variation (CV) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using DSL kits (DSL, Webster, TX). The sensitivity of the assay was 0.8 $\mu\text{g/L}$. The intra-assay CV were 3.4%, 3.0%, and 1.5% for low, medium, and high point on the standard curve, respectively. The interassay CV were 8.2%, 1.5%, and 3.7% for low, medium, and high point of the standard curve. The plasma concentration of the green dye was measured spectrophotometrically. Plasma catecholamines were partially purified by batch alumina extraction (20), separated using ion-pairing reverse-phase high-pressure liquid chromatography ($\mu\text{Bondapak C18}$ -column, Powerline 600A chromatography system, and WISP 700 as autoinjector; Waters Associates, Millipore, Milford, MA), and quantified by a current produced on exposure of the column effluent to oxidizing and then reducing potentials connected in series (Coulchem 5100 A; ESA, Bedford, MA) (21). Recovery through the alumina extraction step, calculated using dihydroxybenzylamine as an internal standard, ranged between 60% and 70%, and each sample was corrected for its recovery. The detection limit for NE was 3 pg. Intra- and interassay variation coefficients were 4.1% and 9.8%, respectively.

Calculations

Forearm plasma flow was estimated by dividing the amount of indocyanine green dye infused by its concentration in the venous plasma and converted to blood flow according to the hematocrit. The forearm balance was calculated by multiplying the arterial-deep vein concentration difference by the forearm blood (glucose) or plasma (NE) flow and was normalized by the forearm volume in liters measured by water displacement. However, in the case of NE, the forearm balance represents the algebraic sum of production and uptake of the neurotransmitter, which have to be measured separately. The forearm fractional extraction (FE) of ^3H -NE was calculated by the equation $\text{FE} = (\text{A}-\text{V})/\text{A}$; where A and V are plasma concentrations of tritiated NE in arterial and venous samples, respectively. NE clearance was obtained by multiplying NE FE by the forearm plasma flow. Forearm NE uptake (FNU) was, thus, obtained according to the formula: $\text{FNU} = \text{NE clearance} \times \text{arterial NE concentration}$. Once FNU was calculated, forearm NE release was obtained subtracting FNU from the net NE balance. For each parameter, the two observations made in the basal state (–15 and 0 min) or during insulin infusion (90 and 120 min) were averaged because, within each condition, there was no statistical difference in the mean values of the various parameters. Statistical analysis to test the effect of insulin was performed by the paired *t* test since only two means were involved. The unpaired *t* test was used to compare normal, with acromegalic subjects. The results are presented as mean \pm SE.

Results

Systolic and diastolic blood pressure were similar in the two groups. Heart rate was 67 ± 2 and 87 ± 3 beats/min in normal subjects and acromegalics, respectively ($P < 0.0001$). In patients with acromegaly serum GH and IGF-I levels were increased far above the normal values.

The data regarding forearm NE kinetics are summarized in Table 2. Arterial plasma NE at rest was similar in control ($197 \pm 28 \text{ pg/mL}^{-1}$) and acromegalic subjects ($200 \pm 27 \text{ pg/mL}^{-1}$), and it increased during insulin stimulation, although the increase reached the statistical significance only in the normal group ($P < 0.05$). NE FE was not different in the two groups and remained substantially unchanged during the hyperinsulinemic period. Forearm NE release at rest was $2.33 \pm 0.55 \text{ ng}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$ in normal subjects and $2.67 \pm 0.61 \text{ ng}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$ in the acromegalic patients. During the hyperinsulinemic period, forearm NE release increased to a similar extent in the two groups (3.13 ± 0.71 and 3.32 ± 0.75

TABLE 1. Clinical characteristics of the subjects

	Normals (n = 8)	Acromegalics (n = 9)
Age (yr)	32 ± 3	35 ± 4
Sex (M/F)	6/2	6/3
BMI (kg/m^{-2})	25 ± 2	28 ± 2
Systolic blood pressure (mm Hg)	128 ± 3	125 ± 4
Diastolic blood pressure (mm Hg)	74 ± 2	80 ± 3
Heart rate (beats/min)	67 ± 2	87 ± 3
Forearm blood flow ($\text{mL}/\text{L}^{-1}\cdot\text{min}^{-1}$)	32 ± 4	30 ± 3
GH ($\mu\text{g}/\text{L}$)		28 ± 11
IGF-I ($\mu\text{g}/\text{L}$)	(100–500) ^a	660 ± 80
Duration of disease (yr)		9 ± 2

^a Range of normal values in subjects aged 20–40 yr in our laboratory.

ng·L⁻¹·min⁻¹ in normals and acromegalics, respectively). The percentage increment was 35% in normals and 27% in acromegalics.

As shown in Table 3, basal blood glucose levels were similar in the two groups and remained virtually unchanged during insulin infusion (CV, <5%). Plasma insulin concentration increased to ~50 μU/mL during insulin infusion in both groups. In the basal state, forearm glucose uptake was 1.1 ± 0.2 and 0.9 ± 0.1 mg·L⁻¹·min⁻¹ in controls and acromegalics, respectively, and, as expected, it increased during insulin stimulation. However, the response observed in the acromegalic patients was markedly blunted as compared with that of control subjects. In normal subjects, there was a 7-fold increase in forearm glucose uptake (7.9 ± 1.3 mg·L⁻¹·min⁻¹) in response to insulin *vs.* a 2-fold increase in acromegalics (2.3 ± 0.4 mg·L⁻¹·min⁻¹; *P* < 0.001).

Discussion

The present study was performed to assess the SNS activity in the skeletal muscle of patients with acromegaly. Previous attempts to explore this issue were based on plasma NE determination or urinary catecholamine excretion (13–17). Given the limitations inherent in the approaches used, those studies cannot be considered conclusive. In the present study, we reexamined the question by using the forearm arterial-venous difference technique in conjunction with the tracer approach to quantify regional NE release. Also, this approach, referred to as NE spillover, provides an index of nerve sympathetic activity because most of the neurotransmitter released from the nerve endings undergoes local degradation or reuptake before reaching the circulation—a process not quantifiable yet. Despite this drawback, forearm NE release is commonly used as a reliable index of SNS activity because it closely reflects sympathetic nerve firing rates.

Our attention was focused on sympathetic outflow to the skeletal muscle for several reasons. First, muscle vascular

bed is an important site of NE release. It has been estimated that as much as 25% of the NE entering plasma in healthy subjects is derived from muscle sympathetic nerves (18). Second, muscle tissue is a major site where catecholamines antagonize the biological action of insulin. Previous studies have shown that epinephrine infusion (9, 22) as well as endogenous sympathetic overactivity (10) are able to reduce insulin-stimulated glucose disposal in forearm tissues, predominantly by β-adrenergic mechanisms. Based on these considerations, we reasoned that an increased sympathetic traffic in skeletal muscle tissue could provide useful insights into the mechanisms underlying some abnormalities commonly associated with acromegaly, particularly insulin resistance and the cardiovascular complications.

The present data demonstrate a normal sympathetic outflow to skeletal muscle in acromegalic patients in the basal state. In this context, noteworthy is a previous study documenting an increased muscle sympathetic activity in patients with GH deficiency by direct recording of sympathetic nerve action potentials at the level of the peroneal nerve (23). This finding suggests that the GH/IGF-I axis is involved in the regulation of the sympathetic drive and, altogether, the data available would indicate that GH normally serves the function to restrain the SNS activity, at least with regard to the skeletal muscle.

During hyperinsulinemia, NE release by the forearm skeletal muscle increased by ≈30%, and the extent of this increase was similar to that achieved in the control group. The possibility that SNS activity may have been differently stimulated in the two groups during the first part of insulin infusion cannot be excluded with certainty. It seems, however, unlikely because insulin-induced SNS activation is not a transient phenomenon, but rather lasts as long as the hormone is infused. Thus, the increment in NE release documented in the last 30 min of insulin infusion closely reflects the sympathetic response of muscle to insulin. Given the fact

TABLE 2. NE kinetics in the forearm skeletal muscle at rest and during insulin stimulation

	Arterial plasma NE (pg/mL ⁻¹)	NE fractional extraction (%)	Forearm NE release (ng·L ⁻¹ ·min ⁻¹)
Normals (n = 8)			
Rest	197 ± 28	70 ± 5	2.33 ± 0.55
Insulin	265 ± 28 ^a	65 ± 5	3.13 ± 0.71 ^a
Acromegalics (n = 9)			
Rest	200 ± 27	60 ± 2	2.67 ± 0.61
Insulin	221 ± 36	51 ± 6	3.32 ± 0.75 ^a

^a *P* < 0.05 as compared with baseline (paired *t* test).

TABLE 3. Glucose metabolism in the forearm skeletal muscle at rest and during insulin stimulation

	Blood glucose (mg/dL)	Plasma insulin (μU/mL)	Forearm glucose uptake (mg·L ⁻¹ ·min ⁻¹)	Forearm blood flow (mL·L ⁻¹ ·min ⁻¹)
Normals (n = 8)				
Rest	88 ± 2	5 ± 1	1.1 ± 0.2	32 ± 4
Insulin	90 ± 2	51 ± 7	7.9 ± 1.3 ^a	35 ± 5
Acromegalics (n = 9)				
Rest	90 ± 5	7 ± 1	0.9 ± 0.1	30 ± 3
Insulin	85 ± 2	46 ± 4	2.3 ± 0.4 ^{a,b}	34 ± 2

^a *P* < 0.0001 as compared with baseline.

^b *P* < 0.001 as compared with controls (unpaired *t* test).

that acromegaly is associated with a strong degree of insulin resistance (6), one may speculate that these patients are exposed daily to frequent bouts of sympathetic overactivity, because of their exaggerated postprandial hyperinsulinemia. It is conceivable that this chronic stimulation of the SNS contributes in the long term to the higher prevalence of cardiovascular complications in acromegaly.

The ability of insulin to activate the SNS is amply recognized (24). Acute physiological hyperinsulinemia selectively stimulates sympathetic nerve outflow to the skeletal muscle, as determined by the measurement of muscle NE release (25) or direct recording of muscle sympathetic nerve activity by microneurography (26). Although the underlying mechanisms are still poorly understood, the available evidence suggests that the insulin sympathoexcitatory effect is mediated by a central neural action involving hypothalamic nuclei. Actually, insulin receptors have been found in several regions of the central nervous system, especially the median hypothalamus (27). In addition, an intracerebroventricular injection of insulin in rats, at a dose devoid of systemic effects, results in increased sympathetic tone (28). Further support to the role of central mechanisms comes from studies by Lembo *et al.* (25), who showed that insulin infused directly into the brachial artery has no effect on NE release and that for a sympathetic activation to occur, insulin has to be infused through a peripheral vein. Of great interest is also the observation that dexamethasone is able to suppress insulin sympathoexcitation, suggesting that the central action of insulin is likely to involve the release of specific neuropeptides, such as CRH (29). The finding of a normal sympathetic response to insulin in acromegalic patients indirectly indicates the absence of hypothalamic abnormalities concerning the CRH-ACTH-cortisol axis, as also supported by the lack of GH paradoxical response to CRH (30) and the normal cortisol rhythm observed in these patients.

In contrast to the ability of insulin to activate the SNS, its stimulatory effect on glucose metabolism is markedly impaired in acromegalic patients. As shown in Table 3, in these patients glucose uptake by the skeletal muscle was 3.5-fold lower than that observed in normal subjects at the same insulin concentrations. The presence of insulin resistance in acromegaly has long been recognized. Already in the 1960s, Galbraith *et al.* (31) documented reduced glucose uptake in forearm tissues during intra-arterial insulin infusion in patients with acromegaly. Subsequently, Moller *et al.* (5) demonstrated that the impaired muscle glucose metabolism is presumably due to a defect in glucose oxidation consequent to the operation of glucose-free fatty acid competition. In addition, a reduced suppressive effect of insulin on hepatic glucose production has also been documented in acromegaly (5).

The finding of a defect in both hepatic and extrahepatic insulin action in acromegalic patients closely resembles the effects of GH infusion in healthy volunteers. An iv 12-h administration of GH blunted the ability of insulin to suppress hepatic glucose production and to stimulate peripheral glucose disposal (32), in line with the view that the derangement in glucose metabolism in acromegaly is, indeed, the consequence of chronic GH excess. Support for this interpretation is also provided by a recent study showing that

transgenic rabbits overexpressing GH develop not only acromegaly but also hyperglycemia, hyperinsulinemia, and hypertriglyceridemia—characteristic manifestations of insulin resistance (33). The present observation of markedly impaired glucose disposal in the presence of normal sympathetic activation by insulin speaks against a role of the SNS in the insulin resistance of acromegaly, which is likely due to GH interference with insulin-promoted cellular events.

The presence of selective resistance to insulin-mediated glucose disposal, but not to the effect of insulin on the SNS observed in acromegalic patients, is reminiscent of similar data obtained by Tack *et al.* (34) in Type II diabetic patients, in whom a marked resistance to the metabolic effects of insulin is associated with a preserved insulin effect on the SNS. This dissociation is not surprising considering that insulin activates a complex array of pathways and mediators. Therefore, it is possible that a defect in insulin signaling may affect some, but not all, insulin actions. These experimental data have their counterpart in some clinical conditions, such as pseudoacromegaly, in which the metabolic effects of insulin are profoundly impaired whereas the mitogenic action is preserved, causing an increased tissue growth (35).

In conclusion, patients with long-term acromegaly show normal sympathetic activity in the skeletal muscle in the basal state and a normal response to the sympathoexcitatory effect of insulin. Thus, the insulin resistance associated with acromegaly is unrelated to adrenergic mechanisms.

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