

Endocrine Role of the Renin-Angiotensin System in Human Adipose Tissue and Muscle. Effect of {beta}-Adrenergic Stimulation

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Endocrine Role of the Renin–Angiotensin System in Human Adipose Tissue and Muscle

Effect of β -Adrenergic Stimulation

Gijs H. Goossens, Johan W.E. Jocken, Ellen E. Blaak, Paul M. Schiffers, Wim H.M. Saris, Marleen A. van Baak

Abstract—The renin–angiotensin system has been implicated in obesity-related hypertension and insulin resistance. We examined whether locally produced components of the renin–angiotensin system in adipose tissue and skeletal muscle play an endocrine role in vivo in humans. Furthermore, the effects of β -adrenergic stimulation on plasma concentrations and tissue release of renin–angiotensin system components were investigated. Systemic renin–angiotensin system components and arteriovenous differences of angiotensin II (Ang II) and angiotensinogen (AGT) across abdominal subcutaneous adipose tissue and skeletal muscle were assessed in combination with measurements of tissue blood flow before and during systemic β -adrenergic stimulation in 13 lean and 10 obese subjects. Basal plasma Ang II and AGT concentrations were not significantly different between lean and obese subjects. Ang II concentrations were increased in obese compared with lean subjects during β -adrenergic stimulation (12.6 ± 1.5 versus 8.1 ± 1.0 pmol/L; $P=0.04$), whereas AGT concentrations remained unchanged. Plasma renin activity increased to a similar extent in lean and obese subjects during β -adrenergic stimulation (both $P<0.01$). No net Ang II release across adipose tissue and skeletal muscle could be detected in both groups of subjects. However, AGT was released from adipose tissue and muscle during β -adrenergic stimulation in obese subjects (both $P<0.05$). In conclusion, locally produced Ang II in adipose tissue and skeletal muscle exerts no endocrine role in lean and obese subjects. In contrast, AGT is released from adipose tissue and muscle in obese subjects during β -adrenergic stimulation, which may contribute to the increased plasma Ang II concentrations during β -adrenergic stimulation in obese subjects. (*Hypertension*. 2007;49:542-547.)

Key Words: angiotensin ■ β -adrenergic receptors ■ obesity ■ renin ■ sympathetic nervous system

Abdominal obesity plays a central role in the metabolic syndrome and is a major risk factor for chronic diseases, such as type 2 diabetes mellitus and cardiovascular disease.¹ Although abdominal obesity is frequently accompanied by hypertension, the mechanisms by which an excess fat mass may lead to hypertension are not fully understood. The renin–angiotensin system (RAS) has been established as a major determinant of blood pressure and cardiovascular disease.² Furthermore, recent clinical trials suggest that blockade of RAS may reduce the incidence of type 2 diabetes.³ Angiotensin II (Ang II), the main effector component of RAS, is produced in the circulation from angiotensinogen (AGT) because of the action of the enzymes renin and angiotensin-converting enzyme. In addition, it has become evident that several components of RAS are present in a variety of tissues, including adipose tissue and skeletal muscle (reviewed in Reference 4), implying that these tissues have the ability to produce Ang II.

There is substantial evidence that circulating RAS components are increased in (hypertensive) obese subjects.^{5–8} In line with this, it has been shown that weight loss reduces systemic RAS activity.⁵ These findings indicate that obesity is responsible for increased systemic RAS activity and suggest that RAS components that are expressed in adipose tissue may also be secreted into the circulation and exert endocrine effects. This idea is supported by a study in wild-type mice, AGT knockout (AGT^{-/-}) mice, and mice specifically expressing AGT in adipose tissue, showing that adipocytes are a considerable source of plasma AGT.⁹

Although less is known about the regulation of RAS, there is evidence that RAS activity is under control of the sympathetic nervous system. It has been shown that β -adrenergic stimulation increases plasma renin activity (PRA) in humans.¹⁰ Furthermore, it has been shown that local β -adrenergic stimulation evokes release of renin and Ang II from forearm vessels in essentially hypertensive subjects.^{11,12} Until now, the effect of

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Subject Characteristics

Characteristic	Lean (n=13)	Obese (n=10)
Age, y	49±3	54±3
Weight, kg	75.2±1.5	101.9±3.2†
BMI, kg/m ²	23.0±0.5	31.9±0.6†
Body fat, %	20.2±1.0	31.7±0.5†
Waist, cm	87.0±1.4	111.5±2.3†
SBP, mm Hg	126.1±3.4	136.6±4.3
DBP, mm Hg	77.3±2.4	85.0±2.7
Fasting glucose, mmol/L	5.3±0.1	5.5±0.2
Fasting insulin, mU/L	7.2±0.6	13.9±1.2*

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are mean±SEM.

* $P=0.001$, † $P<0.001$ vs lean.

β -adrenergic stimulation on local RAS in adipose tissue has not been investigated in vivo in humans.

The objective of the present study was to investigate whether abdominal subcutaneous adipose tissue and skeletal muscle release Ang II and/or AGT into the circulation in vivo in lean and obese subjects. Second, the effects of β -adrenergic stimulation on systemic RAS activity and release of Ang II and AGT from adipose tissue and skeletal muscle were investigated in these subjects.

Methods

Subjects

Thirteen lean (body mass index <25 kg/m²) and 10 obese (body mass index >30 kg/m²), nonsmoking normotensive male subjects participated in this study. Physical characteristics of the subjects are summarized in the Table. Body weight and body fat percentage (hydrostatic weighing) were determined as has been described previously.¹³ All of the subjects were in good health as assessed by medical history, weight stable for ≥ 6 months before investigation, free of any medication, and spent ≤ 3 hours per week in organized sports activities. The medical-ethical committee of Maastricht University approved the study protocol, and all of the subjects gave their written informed consent before participating in the study.

Protocol

All of the subjects were asked to refrain from drinking alcohol and to perform no strenuous exercise for a period of 24 hours before the study. Subjects came to the laboratory by car or bus in the morning after an overnight fast. Four cannulas were inserted before the start of the experiment. Arterialized venous blood was obtained through a cannula inserted retrogradely into a superficial dorsal hand vein. The hand was warmed in a hot box, which was maintained at 60°C to achieve adequate arterialization.¹⁴ In the same arm, a second cannula was inserted in a forearm antecubital vein for the infusion of the nonselective β -adrenergic agonist isoprenaline (ISO). In the contralateral arm, a third catheter was introduced retrogradely in an antecubital vein of the forearm for sampling of deep venous blood, draining skeletal muscle. Finally, after identification of the veins with a fiber-optic light source, a 10-cm 22-gauge catheter (central venous catheter kit, Seldinger technique, Becton Dickinson BV) was introduced anterogradely over a guide wire into one of the superficial veins on the anterior abdominal wall and threaded toward the groin, so that its tip lay just superior to the inguinal ligament, to obtain adipose tissue venous blood.¹⁵ This provides the drainage from the adipose tissue of the abdomen, uncontaminated by muscle drainage and with only a minor contribution from skin.¹⁵⁻¹⁷ The adipose vein was kept patent by continuous saline (9 g/L NaCl) infusion at a rate of 80 mL/h. The subjects rested in a supine position for the duration of the study.

Ang II and AGT Release Into the Circulation

Circulating Ang II and AGT concentrations and net release of these RAS components from abdominal subcutaneous adipose tissue and skeletal muscle into the circulation were investigated in vivo under baseline conditions and during intravenous infusion of ISO. After a 120-minute baseline period, ISO was intravenously infused at a rate of 20 ng kg fat free mass⁻¹ min⁻¹ for 60 minutes.¹⁸ During the experiment, heart rate was recorded continuously by means of a 3-lead ECG. When heart rate increased >40 bpm or in case of ECG irregularities, ISO infusion was discontinued (n=2, 1 lean and 1 obese subject).

Blood samples were taken simultaneously from the arterialized vein, the adipose vein, and the deep forearm vein while the hand circulation was occluded at 3 baseline time points (t90, t105, and t120) and 3 time points during the last 30 minutes of ISO infusion (t160, t175, and t190). Adipose tissue blood flow was monitored continuously using ¹³³xenon washout,¹⁹ and forearm blood flow (FBF) was measured at the same time points that blood was collected using venous occlusion plethysmography,²⁰ as has been described previously. Plasma flow was calculated as tissue blood flow \times (1-hematocrit), with hematocrit expressed as a fraction. Ang II and AGT fluxes across adipose tissue and muscle were calculated from the arteriovenous concentration differences multiplied by tissue plasma flow. Positive fluxes indicate net uptake from plasma, whereas negative fluxes indicate net tissue release.

Analyses

Blood samples were collected into syringes containing either EDTA or Ang II buffer²¹ and immediately transferred into ice-chilled polypropylene tubes. Blood samples were then centrifuged (1000g, 4°C, 10 minutes), and plasma was immediately frozen in liquid nitrogen and stored at -80°C until analysis. A small proportion of blood was used for measurement of oxygen saturation to ensure adequate arterialization (ABL 510, Radiometer).

Ang II was measured by a standard radioimmunoassay (Peninsula Laboratories Europe) after C-18 Sep-Pak (Waters-Millipore) extraction of the peptide. Intra-assay and interassay coefficients of variation were 4.6% and 7.7%, respectively. AGT was measured by radioimmunoassay of Ang I after complete hydrolysis with an excess of human renin. Briefly, 25 μ L of plasma prediluted 1:100 in assay buffer was incubated together with 470 μ L of 0.15 mol/L citrate-phosphate buffer (pH 5.7) containing 0.025 mol/L of Na₂-EDTA, 1.0 g/L of BSA, and 50 ng of human recombinant renin with 5 μ L of PMSF for 60 minutes at 37°C. Reactions were stopped by incubation on ice, and the amount of Ang I generated was measured. AGT concentration is expressed as nanograms of Ang I per milliliter. Active renin was measured by a standard radioimmunometric assay (Renin III generation, Schering CIS Bio International). Intra-assay and interassay coefficients of variation were 2.9% and 7.6%, respectively. Plasma glucose concentration was measured using a standard enzymatic method (ABX Pentra Glucose HK CP, Radiometer). Plasma insulin concentration was measured by a specific double antibody radioimmunoassay for human insulin (Linco Research Inc).

Statistical Analysis

Data are presented as mean±SEM. Differences between lean and obese subjects were compared using the Mann-Whitney test. The effects of β -adrenergic stimulation within groups were tested using Wilcoxon signed-rank test. Calculations were done using SPSS 10.1 for Windows. $P<0.05$ was considered to be statistically significant.

Results

By definition, obese subjects had a significantly higher body weight, body mass index, and body fat percentage compared with lean subjects, as summarized in the Table.

Adipose Tissue Blood Flow and FBF

Basal adipose tissue blood flow was significantly higher in lean compared with obese subjects (2.2±0.2 versus 1.4±0.2

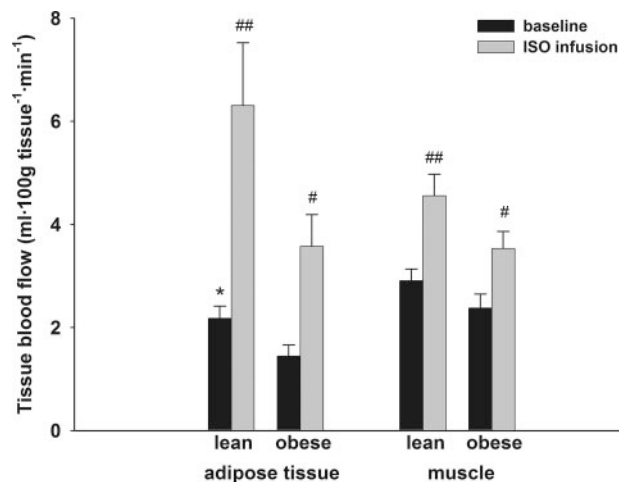


Figure 1. Adipose tissue (lean, $n=9$; obese, $n=7$) and muscle blood flow (lean, $n=13$; obese, $n=10$) under baseline conditions and during β -adrenergic stimulation (ISO infusion). * $P<0.05$ vs obese, # $P<0.05$ vs baseline, ## $P<0.01$ vs baseline. Values are mean \pm SEM.

mL 100 g tissue⁻¹ min⁻¹, $P=0.03$, respectively), whereas basal FBF was comparable in lean and obese subjects (2.9 ± 0.2 versus 2.4 ± 0.3 mL 100 mL forearm tissue⁻¹ min⁻¹, $P=0.28$, respectively; Figure 1).

β -Adrenergic stimulation induced a significant increase in tissue blood flows. Adipose tissue blood flow significantly increased during β -adrenergic stimulation compared with baseline in both lean (6.3 ± 1.2 versus 2.2 ± 0.2 mL 100 g tissue⁻¹ min⁻¹, $P=0.008$, respectively) and obese subjects (3.6 ± 0.6 versus 1.6 ± 0.2 mL 100 g tissue⁻¹ min⁻¹, $P=0.03$, respectively). Furthermore, FBF was significantly elevated during β -adrenergic stimulation in both lean (4.6 ± 0.4 versus 2.9 ± 0.2 mL 100 mL forearm tissue⁻¹ min⁻¹; $P=0.002$) and obese subjects (3.5 ± 0.3 versus 2.5 ± 0.3 mL 100 mL forearm tissue⁻¹ min⁻¹; $P=0.01$; Figure 1). The increase in adipose tissue blood flow and FBF during β -adrenergic stimulation was not significantly different between groups ($P=0.22$ and $P=0.46$, respectively).

Plasma Ang II and AGT Concentrations

Basal plasma Ang II concentrations were not significantly different between lean ($n=13$) and obese ($n=10$) subjects (8.2 ± 1.3 versus 9.9 ± 0.9 pmol/L, $P=0.21$, respectively). β -Adrenergic stimulation had no significant effect on circulating Ang II concentrations in lean ($n=12$) subjects ($P=0.13$) but increased Ang II concentrations in obese ($n=9$) subjects (baseline: 10.2 ± 0.9 versus ISO: 12.6 ± 1.5 pmol/L; $P=0.05$), resulting in significantly higher Ang II concentrations during β -adrenergic stimulation in obese compared with lean subjects ($P=0.04$; Figure 2A). Plasma AGT concentrations were not significantly different between lean and obese subjects at baseline (617.1 ± 107.0 versus 657.9 ± 122.4 ng of Ang I per milliliter, $P=0.71$, respectively) and during β -adrenergic stimulation (569.9 ± 111.1 versus 656.2 ± 136.4 ng of Ang I per milliliter, $P=0.59$, respectively; Figure 2B).

PRA

Basal PRA was comparable between lean and obese subjects (12.8 ± 1.8 versus 10.8 ± 1.7 mU/L, $P=0.77$, respectively).

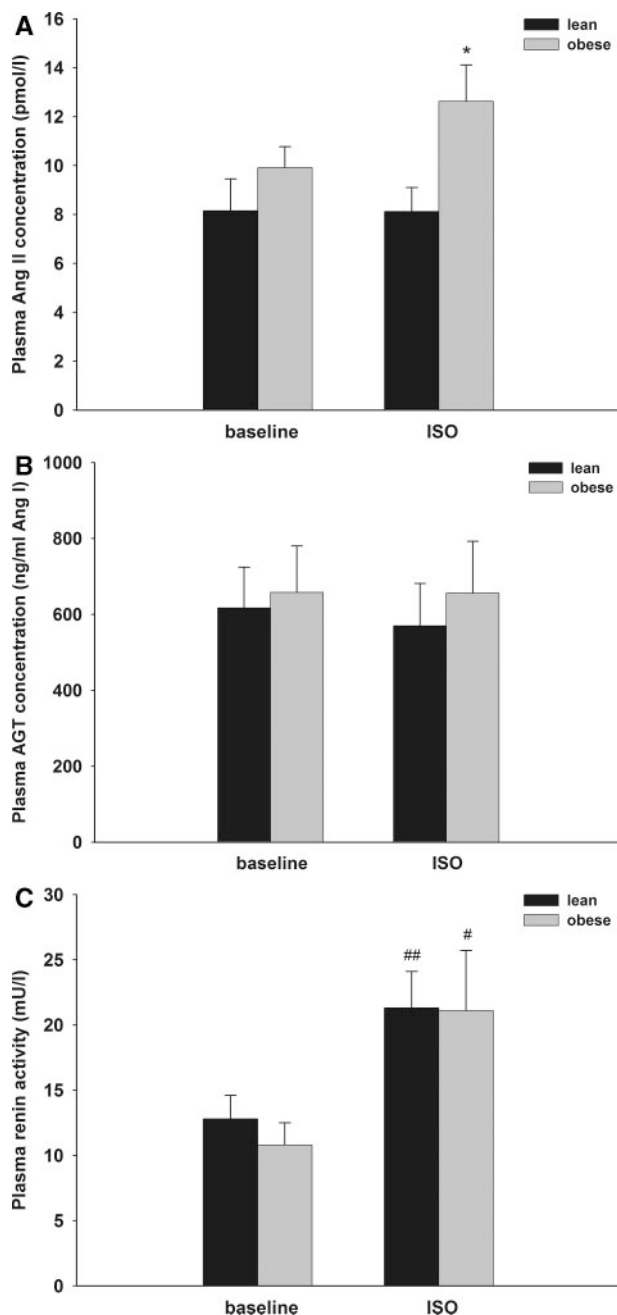


Figure 2. (A) Plasma Ang II concentrations, (B) plasma AGT concentrations, and (C) plasma renin activity in lean ($n=13$) and obese ($n=10$) subjects under baseline conditions and during β -adrenergic stimulation (ISO infusion; $n=12$ and $n=9$, respectively). * $P<0.05$ vs lean, # $P=0.01$ vs baseline, ## $P<0.01$ vs baseline. Values are mean \pm SEM.

PRA was significantly increased from baseline during β -adrenergic stimulation in lean (21.3 ± 2.8 mU/L; $P=0.002$) and obese subjects (21.1 ± 4.6 mU/L; $P=0.01$; Figure 2C). The increase in PRA during β -adrenergic stimulation was not different between groups ($P=0.94$).

Ang II and AGT Fluxes Across Abdominal Subcutaneous Adipose Tissue

Under baseline conditions, no significant net uptake or release of Ang II across abdominal subcutaneous adipose tissue

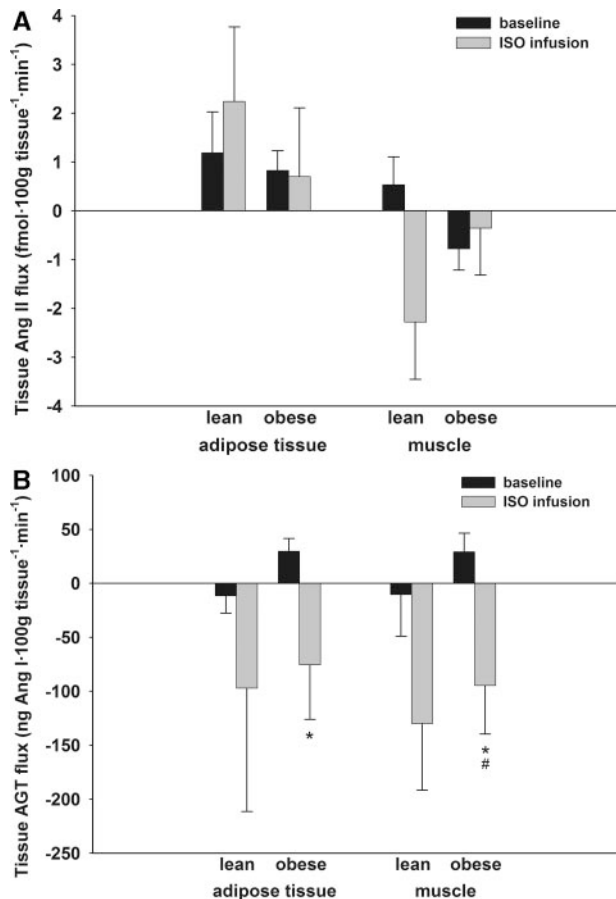


Figure 3. (A) Ang II fluxes and (B) AGT fluxes across abdominal subcutaneous adipose tissue (lean, $n=9$; obese, $n=7$) and skeletal muscle (lean, $n=13$; obese, $n=10$) under baseline conditions and during β -adrenergic stimulation (ISO infusion). Positive fluxes indicate net uptake from plasma, whereas negative fluxes indicate net tissue release. * $P<0.05$ vs baseline, # $P<0.05$ vs 0 flux. Values are mean \pm SEM.

could be detected in lean (1.18 ± 0.84 fmol 100 g tissue⁻¹ min⁻¹, $P=0.14$ versus zero flux) and obese subjects (0.83 ± 0.41 fmol 100 g tissue⁻¹ min⁻¹, $P=0.18$ versus zero flux; Figure 3A). Net Ang II fluxes across adipose tissue were not significantly different from baseline during β -adrenergic stimulation in lean ($P=0.52$) and obese subjects ($P=0.75$; Figure 3A).

No significant baseline net uptake or release of AGT across abdominal subcutaneous adipose tissue was observed in lean (-11.6 ± 16.1 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.59$ versus 0 flux) and obese subjects (29.6 ± 12.0 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.06$ versus zero flux; Figure 3B). β -Adrenergic stimulation induced a shift from a tendency for AGT uptake toward net AGT release across abdominal subcutaneous adipose tissue, which was statistically significant in obese (baseline: 34.8 ± 12.8 versus ISO: -75.5 ± 50.6 ng Ang I 100 g tissue⁻¹ min⁻¹; $P=0.03$) but not in lean subjects ($P=0.77$; Figure 3B).

Ang II and AGT Fluxes Across Skeletal Muscle

There was no detectable net uptake or release of Ang II across skeletal muscle under baseline conditions in lean (0.53 ± 0.57 fmol 100 g tissue⁻¹ min⁻¹, $P=0.55$ versus zero flux) and

obese subjects (-0.78 ± 0.44 fmol 100 g tissue⁻¹ min⁻¹, $P=0.07$ versus zero flux; Figure 3A). β -Adrenergic stimulation had no significant effect on net Ang II fluxes across muscle in lean ($P=0.21$) and obese subjects ($P=0.59$; Figure 3A).

No AGT release across muscle was detectable at baseline in lean (-10.4 ± 38.7 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.46$ versus zero flux) and obese subjects (29.1 ± 17.3 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.16$ versus zero flux; Figure 3B). However, β -adrenergic stimulation evoked release of AGT across muscle in lean (-130.0 ± 61.7 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.05$ versus zero flux) and obese subjects (-94.7 ± 45.0 ng Ang I 100 g tissue⁻¹ min⁻¹, $P=0.02$ versus zero flux), with no significant differences between groups (Figure 3B).

Discussion

There is substantial evidence that obesity is a prime cause of hypertension, cardiovascular disease, and insulin resistance in obese individuals.^{1,22} Many studies suggest that RAS in adipose tissue may play an important role in the development of obesity-associated hypertension and insulin resistance.⁴ We hypothesized that locally generated RAS components in adipose tissue and/or skeletal muscle are released into the circulation and may act as endocrine hormones. Furthermore, the effects of β -adrenergic stimulation on systemic RAS activity and local Ang II and/or AGT release from adipose tissue and skeletal muscle were examined. We demonstrated that plasma Ang II concentrations are increased during β -adrenergic stimulation in obese but not in lean subjects. Increased release of AGT from adipose tissue and skeletal muscle in obese subjects during β -adrenergic stimulation may explain this finding.

Circulating RAS Components

We found that fasting plasma Ang II and AGT concentrations are comparable between lean and obese subjects. The comparable plasma Ang II concentrations between both groups are in line with previous findings.⁵ In contrast, most studies have shown increased plasma AGT concentrations in obese subjects.⁵⁻⁸ However, the increased AGT concentrations in obese subjects were not significantly different in lean and obese subjects after adjustment for blood pressure.⁸ Although body mass index was positively associated with blood pressure in the present study (data not shown), the blood pressure difference was not significant between groups, which may explain the comparable plasma AGT concentrations in lean and obese subjects. β -Adrenergic stimulation increased plasma Ang II concentrations in obese but not in lean subjects, whereas plasma AGT concentrations remained unchanged in both groups.

It has been demonstrated previously that β -adrenergic stimulation increases PRA in humans.^{10,23-25} Until now, it was unknown whether the effect of β -adrenergic stimulation on PRA is comparable between lean and obese subjects. We show that PRA was increased to a similar extent in both groups of subjects during intravenous infusion of the non-selective β -adrenergic agonist ISO. These data suggest that the increase in PRA cannot explain the elevated plasma

Ang II concentration in obese subjects during β -adrenergic stimulation.

Endocrine Function of the Local RAS in Adipose Tissue and Skeletal Muscle

Because adipose tissue exerts endocrine functions²⁶ and RAS components are expressed in human adipose tissue,^{4,5} it is tempting to speculate that secretion of RAS components from adipose tissue could play a role in obesity-related complications, including hypertension. A recent report demonstrated that 5% weight loss was accompanied by decreased systemic RAS activity and blood pressure,⁵ which further suggests that obesity is responsible for increased systemic RAS activity. The concept that RAS components that are expressed in adipose tissue may exert endocrine effects is supported by a study where wild-type mice were compared with AGT^{-/-} mice and with transgenic mice specifically expressing AGT in adipose tissue either on the AGT^{-/-} background or on the wild-type background. It was shown that adipocytes are a considerable source of plasma AGT, which may explain the observed elevated blood pressure in the transgenic animals.⁹ Likewise, a local Ang II generating system is present in skeletal muscle,²⁷ and this tissue may, therefore, also contribute to circulating concentrations of RAS components.

Determination of Ang II fluxes across abdominal subcutaneous adipose tissue and muscle under baseline conditions and during β -adrenergic stimulation revealed that there was no detectable net uptake or release of Ang II across adipose tissue and skeletal muscle in lean and obese subjects under both conditions. Therefore, Ang II secretion from these tissues cannot explain the increased Ang II concentrations observed in obese subjects during β -adrenergic stimulation. Because it is well established that Ang II is produced by human adipocytes,²⁸ our data suggest that locally produced Ang II in adipose tissue acts as an autocrine and/or paracrine hormone and does not exert endocrine effects. The present findings seem to be in contrast with a recent study demonstrating Ang II secretion from adipose tissue in vivo in overweight/obese subjects.²⁹ However, when measuring Ang II, it is crucial to use Ang II buffer to eliminate breakdown, as well as further production, of Ang II during processing of the samples.^{21,30} In the study by Harte et al,²⁹ these strict methodologic procedures were not taken into account. This may explain the reported supraphysiological Ang II concentrations and raises some doubt on the validity of these findings. Our muscle data are in line with previous findings demonstrating that Ang II is not released from skeletal muscle under baseline conditions in hypertensive patients.¹² However, local β -adrenergic stimulation evoked renin and Ang II release from forearm vessels in these patients,^{11,12} which seems to be in contradiction with our findings of no detectable Ang II release. Several explanations may be responsible for this apparent discrepancy. First, local β -adrenergic stimulation (intrabrachial infusion)¹² may have caused a more pronounced stimulus compared with intravenous infusion of a β -adrenergic agonist in the present study.¹⁸ This is supported by the fact that the increase in FBF during local β -adrenergic stimulation was more pronounced than the elevation in FBF observed in the present study. Second, they studied hyperten-

sive and moderately sodium-depleted subjects,^{11,12} characterized by increased activation of the RAS,³¹ whereas the subjects in the present study were normotensive and maintained their normal dietary sodium intake. Third, the release of renin and Ang II across skeletal muscle during local β -adrenergic stimulation rapidly declined after 5 to 10 minutes,¹² indicating that this system might represent a short-term control mechanism. Because in the present study Ang II release was assessed during the last 30 minutes of a 1-hour ISO infusion, downregulation of local Ang II generation may have occurred, resulting in undetectable Ang II release from muscle.

Furthermore, we did not find AGT release across adipose tissue and skeletal muscle under baseline conditions. However, AGT was released from skeletal muscle in lean (tendency) and obese subjects during β -adrenergic stimulation. In addition, a significant shift toward net AGT secretion from adipose tissue was observed in obese subjects during ISO infusion. Net AGT release across adipose tissue and skeletal muscle shows high interindividual variation in lean subjects. Importantly, mean net AGT release across adipose tissue during β -adrenergic stimulation in lean subjects is largely explained by 1 individual showing high AGT release across adipose tissue. If we had decided to leave this individual out of the statistical analysis, the mean value for net AGT release across adipose tissue would have been slightly positive (direction of net AGT uptake), and the SE would have been much smaller (from -97.1 ± 114.3 to 15.6 ± 21.2 ng of Ang I 100 g tissue⁻¹ min⁻¹). However, there was no reason to leave this subject out of the statistical analysis. Considering the increased adipose tissue and skeletal muscle mass in obese compared with lean subjects (Table), these data suggest that at the whole body level AGT release from adipose tissue and skeletal muscle may contribute to the increased plasma Ang II concentrations during β -adrenergic stimulation in obese subjects. Rapid conversion of AGT that is released from adipose tissue and skeletal muscle into Ang I and subsequent conversion into Ang II may explain why plasma AGT concentrations were not increased during β -adrenergic stimulation. An additional explanation may be that increased Ang II production and secretion from other tissues than abdominal subcutaneous adipose tissue and skeletal muscle, such as the kidney and liver, is responsible for this elevation in Ang II concentration. In addition, visceral fat may produce and secrete Ang II and/or AGT, because AGT mRNA expression is increased in visceral compared with subcutaneous adipose tissue.^{32,33}

Perspectives

The present findings demonstrate that net Ang II uptake or release across abdominal subcutaneous adipose tissue and skeletal muscle is undetectable under baseline conditions and during β -adrenergic stimulation. Because Ang II is produced by human adipocytes, our data suggest that locally produced Ang II in adipose tissue acts as an autocrine and/or paracrine hormone. In contrast, AGT is released from adipose tissue and skeletal muscle in obese subjects during β -adrenergic stimulation, and this may contribute to the observed increase in plasma Ang II concentrations during β -adrenergic stimulation in

these subjects. Although we recognize that β -adrenergic stimulation is different from sympathetic nervous system activity (resulting in α -adrenergic and β -adrenergic stimulation) and we have not measured sympathetic nervous system activity in the present study, it is tempting to postulate that activation of the local adipose tissue and muscle RAS is an important mechanism by which increased sympathetic nervous system activity may contribute to the development of hypertension in obesity. Our findings further suggest that angiotensin-converting enzyme inhibitors may exert their beneficial effects, at least partly, by decreasing the conversion of adipose tissue and muscle-derived AGT, thereby reducing Ang II production.

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Disclosures

None.

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