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Low Dietary Sodium and Exogenous Angiotensin II Infusion Decrease Plasma Adiponectin Concentrations in Healthy Men

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Content: Adiponectin has antiinflammatory and vascular protective effects and may improve insulin sensitivity. Animal data suggest a role of the renin-angiotensin aldosterone system (RAAS) in the regulation of adiponectin.

Objective: Our objective was to investigate the role of the RAAS in regulation of adiponectin in humans *in vivo*. To this purpose we studied the effects of physiological (change in sodium status) and pharmacological modulation of RAAS activity (angiotensin II infusion and enalapril treatment) on plasma adiponectin.

Design, Setting, and Patients: Thirty-five healthy male volunteers (aged 26 ± 9 yr) were studied after two 7-d periods: one on a low-sodium diet (LS, 50 mmol Na^+ per day) and one on a high-sodium diet (HS, 200 mmol Na^+ per day). At the end of each period, adiponectin was measured, and its response to angiotensin II infusion (0.3, 1, and 3 ng/kg·min all during 1 h) was determined. Additionally, all subjects received 1 wk treatment of enalapril 20 mg once daily (angiotensin converting enzyme inhibition) during the HS.

Main Outcome Measure: We measured plasma adiponectin concentrations during LS and HS and in response to angiotensin II infusion.

Results: The suppression of the RAAS by HS elicited a significant rise in adiponectin [LS baseline, 11.9 (8.3–16.2) μg/liter; HS baseline, 14.4 (11.2–20.4) μg/liter; $P < 0.05$]. All doses of angiotensin II elicited a profound decrease in adiponectin during both conditions [LS 3 ng/kg·min, 7.4 (6.3–8.9) μg/liter; HS 3 ng/kg·min, 8.4 (7.3–9.9) μg/liter; both $P < 0.001$ *vs.* baseline]. Angiotensin converting enzyme inhibition induced a significant rise in adiponectin [16.6 (10.6–20.9) μg/liter, $P < 0.05$ *vs.* HS].

Conclusion: Physiological and pharmacological modulation of RAAS affects plasma adiponectin with lower concentrations during the high angiotensin II conditions. The therapeutic potential of RAAS blockade as a tool to correct hypoadiponectinemia should be explored further.
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ADIPONECTIN IS SPECIFICALLY and abundantly produced in adipose tissue and has direct effects on glucose and lipid metabolism (1). The antiinflammatory and cardioprotective properties of this adipokine are increasingly recognized. Adiponectin circulates in plasma at high concentrations (2). Plasma adiponectin concentrations are inversely associated with insulin resistance and obesity. Furthermore, lower concentrations of adiponectin have been described in type 2 diabetes mellitus. Low adiponectin concentrations have also been documented in subjects with essential hypertension and may predict incident cardiovascular disease.

Furthermore, lower concentrations of adiponectin are associated with an increased risk for the development of diabetes (3, 4), essential hypertension (5), and myocardial infarction (6). These associations are attributed to antiatherogenic actions of adiponectin as well as its favorable effects on insulin sensitivity (7).

The mechanisms involved in the regulation of plasma adiponectin are of considerable interest but are largely unknown. Several factors have been proposed to determine plasma adiponectin, such as its renal clearance (8) and activation of the peroxisome proliferator-activated receptor-γ (9). Plasma adiponectin concentrations have been shown to be up-regulated by thiazolidinediones (10). They have been proposed to ameliorate insulin resistance by binding and activating peroxisome proliferator-activated receptor-γ in adipose tissue, thereby promoting adipocyte differentiation and increasing the number of small adipocytes that are more sensitive to insulin (11).

Interestingly, in diabetic (12) and hypertensive patients (13), inhibition of the renin-angiotensin aldosterone system (RAAS) by angiotensin receptor type 1 blockade or angiotensin converting enzyme inhibition (ACEi) increases plasma adiponectin. Moreover, very recently infusion of angiotensin II (ang II) in rats was shown to decrease adiponectin concentrations, and this response was prevented by ang II receptor blockade (14). These observations elicit the hypothesis that the RAAS is involved in regulation of adiponectin in humans.

To test this hypothesis, we studied the effects of physio-

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Abbreviations: ACEi, Angiotensin converting enzyme inhibition; ang II, angiotensin II; GFR, glomerular filtration rate; HMW, high molecular weight; HOMA, homeostasis model assessment; HS, high-sodium diet; LS, low-sodium diet; MAP, mean arterial pressure; PRA, plasma renin activity; RAAS, renin-angiotensin aldosterone system.

logical and pharmacological modulation of the RAAS on plasma adiponectin in healthy subjects. Physiological modulation of RAAS activity was induced by a shift in dietary sodium intake. Pharmacological modulation was achieved by infusion of exogenous ang II (stimulation) on both high and low sodium intake and angiotensin converting enzyme inhibition (ACEi) during high sodium intake.

Subjects and Methods

Subjects

Thirty-five healthy men (age, 26 ± 9 yr, mean ± SD) were recruited for the study. They were normotensive, defined as sitting systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 80 mm Hg. All subjects underwent normal routine physical examination. Exclusion criteria were any abnormalities during routine physical examination, a body mass index more than 30 kg/m^2, diabetes mellitus, and drug use. Written informed consent was obtained from each subject after a full explanation of the study. The study protocol was approved by the Ethics Committee of the University Medical Center Groningen.

Study protocol

The protocol consisted of two periods in which all the subjects were first studied after a 7-d period on a low-sodium diet (LS, with an aim of 50 mmol/d) and afterward a 7-d period on a high-sodium diet (HS, with an aim of 200 mmol/d). The diets were based on personal food habits. We achieved differences in sodium intake by replacing sodium-rich products with a low-sodium product of the product group to remain isocaloric with a similar balance between protein, carbohydrate, and fat. On d 4 and 6 of each dietary period, subjects collected 24-h urine to assess dietary compliance and achievement of a stable sodium balance.

On d 7, the subjects reported to the research unit at 0800 h after an overnight fast. Body weight, length, waist, and hip values were measured. An iv canula was inserted into each forearm, one for drawing blood samples, the other for infusion of ang II and renal function tracers. Subjects remained in a semisupine position after a light standardized breakfast in a quiet room for 3 h to standardize their activities and posture before the ang II infusion and blood sampling. We measured blood pressure at 15-min intervals using a noninvasive device (Dinamap; GE Medical Systems, Milwaukee, WI).

Glomerular filtration rate (GFR)

GFR was measured by constant infusion of radioactive-labeled tracers [^{125}I]iothalamate (Tyco Health Care, Petten, The Netherlands) and [^{131}I]hippurate (QOL Medical, Woodinvill, WA), respectively, as previously described (15). After drawing a blank blood sample, a priming solution containing 0.4 ml/kg body weight of the infusion solution (0.04 MBq of [^{125}I]iothalamate and 0.03 MBq of [^{131}I]hippurate) plus an extra of 0.6 MBq of [^{125}I]iothalamate was given at 0800 h, followed by infusion at 12 ml/h. To attain stable plasma concentration of both tracers, a 2-h stabilization period followed, after which baseline measurements started at 1000 h. The clearances were calculated as (U∗V)/P and (I∗V)/P, respectively, where U∗V represents the urinary excretion of the tracer, I∗V represents the infusion rate of the tracer, and P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space by multiplying the urinary clearance of [^{125}I]iothalamate with the ratio of the plasma and urinary clearance of [^{131}I]hippuran (15).

Ang II infusion

Baseline values for blood pressure were obtained from 1000–1200 h. Between 1200 and 1500 h, ang II (Clinalfa; Merck Biosciences AG, Läufelfingen, Switzerland) was administered in the left antecubital vein. Between 1200 and 1300 h, ang II was infused at a constant rate in a dose of 0.3 ng/kg·min. Thereafter, ang II was infused at a constant rate of 1 ng/kg·min and 3 ng/kg·min each for 1 h. At the end of each infusion step (at 1300, 1400, and 1500 h), blood samples were drawn. During the ang II infusions, blood pressure was measured at 5-min intervals.

ACEi

Additionally all subjects received 1 wk of enalapril 20 mg once daily (ACEi) while on HS (200 mmol/d). At the end of the week, blood samples were drawn for adiponectin measurement, and blood pressure was measured by Dinamap.

Blood sampling and analysis

Blood samples for baseline assessment of adiponectin were drawn at 1100 h. Samples were drawn in semisupine position in prechilled tubes and immediately centrifuged at 4 C. Plasma and serum for measurement of adiponectin, aldosterone, renin activity, and insulin was stored at −20 C until analysis. Aldosterone was measured with a commercially available RIA kit (Diagnostic Products Corp., Los Angeles, CA). Plasma renin activity (PRA) was measured as described previously with a RIA that detects the amount of angiotensin I produced per hour in the presence of excess angiotensinogen (nanograms of angiotensin I produced per milliliter of plasma per hour). This assay measures the enzymatic activity of active plasma renin in the presence of an exogenous excess of its substrate (16). Fasting serum insulin was determined using a radioactive immunoassay (DSL-1600; Diagnostic Systems Laboratories, Webster, TX). Plasma glucose was determined by the glucose oxidase method (YSI 2300 Stat plus; YSI, Yellow Springs, OH). Homeostasis model assessment (HOMA) was calculated by [glucose (in millimoles per liter) × insulin (in microunits per milliliter)/22.5.

Blood samples for determination of ang II were drawn in cold, standard 3-ml vacuum tubes containing 5.4 μg K_3EDTA and an additional 0.2 ml ACE inhibitor cocktail containing 1.704 μg phenanthroline, 0.16 mg enalapril, 1 ml ethanol, and 4 mg neomycin. After centrifugation at 4 C, the plasma for determination of ang II was snap-frozen and stored at −80 C until analysis. Plasma concentration of ang II was measured by a specific RIA after Sep-Pak extraction of plasma samples and HPLC separation (17). Plasma adiponectin and leptin were measured by ELISAs using a kit from Linco Research Inc. (St. Charles, MO; catalog no. EZHADP-61K). Within-assay coefficients of variation for adiponectin and leptin were 3.4 and 3.7%, respectively.

Data analysis

Mean values and SD were calculated for normally distributed variables after checking for normality. Medians and quartiles were computed for variables with nonnormal distribution. After testing for normality, we used Student's paired *t* test or Wilcoxon signed rank test to compare values between the different periods, each subject being its own control. A value of $P < 0.05$ was considered to be statistically significant.

Results

Effects of altered sodium status

The 35 healthy male subjects had a BMI of 22.5 (21.2–24.4) kg/m^2 and waist circumference was 81 (76–85) cm. Urinary sodium excretion was consistent with good dietary compliance at both sodium intakes, as shown in Table 1. HS induced a small but significant rise in weight and blood pressure. HS also elicited an increase in GFR.

The effects on PRA and aldosterone are given in Table 2.

TABLE 1. Clinical parameters

	Low sodium	High sodium
U_{Na24} (mmol/24 h)	40 ± 25	219 ± 56[a]
Body weight (kg)	79.1 ± 9.4	80.4 ± 9.5[a]
MAP (mm Hg)	85 ± 7	88 ± 8[a]
GFR (ml/min·1.73 m^2)	103 (99–113)	110 (104–120)[b]

Data are expressed as mean ± SD or median (25th and 75th percentile). GFR was measured with [^{125}I]iothalamate. U_{Na24}, 24-h urinary sodium excretion.

[a] $P < 0.05$ for LS *vs.* HS (Student's paired *t* test).

[b] $P < 0.05$ for LS *vs.* HS (Wilcoxon signed rank test).

TABLE 2. Circulating values of RAAS components, glucose, insulin, and insulin sensitivity

	Low sodium	High sodium
PRA (ng ang I/ml·h)	5.9 (4.4–8.1)	2.5 (1.6–3.5)[a]
Aldosterone (ng/liter)	130 (81–174)	43 (24–57)[a]
Glucose (mg/dl)	4.5 (4.1–4.9)	4.5 (4.2–4.8)
Insulin (μU/ml)	8.3 (6.1–13.5)	8.0 (6.3–11.6)
HOMA	1.7 (1.3–2.5)	1.6 (1.2–2.4)

Data are expressed as median (25th–75th percentile). HOMA was calculated as glucose × insulin/22.5.

[a] $P < 0.05$ for low *vs.* high sodium (Wilcoxon signed rank test).

The shift from LS to HS intake suppressed PRA and aldosterone concentration significantly to approximately one third of the values on LS. The shift in sodium intake did not affect glucose or insulin concentration or the HOMA index.

The shift from LS to HS suppressed ang II concentration in proportion to the decreases in PRA and aldosterone (Fig. 1, *left* y-axis). HS elicited a significant rise in adiponectin by 21% from 11.9 (8.3–16.2) to 14.4 (11.2–20.4) μg/liter (Fig. 1, *right* y-axis). During baseline, ang II levels did not correlate with adiponectin levels. The changes in circulating ang II concentrations were thus mirrored by those in adiponectin.

Ang II infusion

Ang II infusion induced a dose-dependent significant increase in mean arterial pressure (MAP) (Fig. 2, *left panel*) during both LS and HS. During LS, the lowest dose of ang II did not induce a significant rise in MAP (LS baseline *vs.* 0.3 ng ang II, $P = 0.45$). During both LS and HS, all other doses of ang II induced a significant rise in MAP compared with the MAP at the preceding lower rate of infusion ($P < 0.001$). Plasma adiponectin concentrations (Fig. 2, *right panel*) decreased significantly (LS/HS baseline *vs.* 0.3, 1, and 3 ng, $P < 0.001$) during all steps of ang II infusion compared with baseline, during both LS and HS, with a prominent decrease during the lowest dose of ang II already. Figure 3 shows the changes from baseline in blood pressure and adiponectin during ang II infusion (3 ng/kg) on the two different sodium intakes, allowing a comparison of the ang II responses on LS and HS. As anticipated, the overall blood pressure response to ang II was higher during HS (Δ MAP, LS *vs.* HS, $P < 0.05$). Likewise, the overall decrease in adiponectin was larger during HS as well (Δ adiponectin, LS *vs.* HS, $P < 0.05$).

ACEi

MAP decreased significantly during ACEi (88 ± 8 *vs.* 83 ± 8 mm Hg, $P < 0.05$). ACEi induced a significant rise in adiponectin [14.4 (11.2–20.4) *vs.* 16.6 (10.6–20.9) μg/liter, $P < 0.05$].

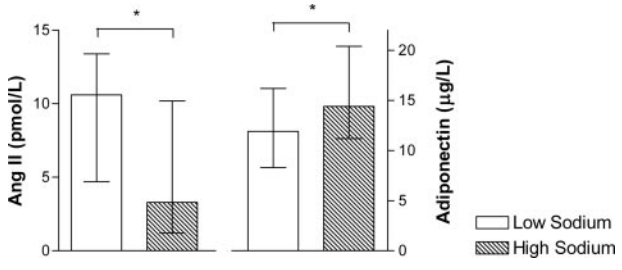

FIG. 1. Plasma ang II and adiponectin. Data are expressed as median (25th and 75th percentile). *, $P < 0.05$ for LS *vs.* HS (Wilcoxon signed rank test).

Leptin

Sodium intake did not significantly affect leptin concentrations (Fig. 4). During LS, ang II infusion did not influence leptin concentrations. However, during HS, there was a small but significant decrease in leptin concentrations during ang II infusion.

Discussion

This is the first study that shows that physiological suppression of ang II by HS and ACEi is associated with an increase in plasma adiponectin concentrations. Moreover, plasma adiponectin is profoundly decreased by infusion of exogenous ang II. Thus, physiological and pharmacological modulation of ang II is associated with reciprocal changes in adiponectin concentrations. Together, these findings support the hypothesis that the RAAS contributes to a relevant extent in plasma adiponectin regulation in humans *in vivo*, most likely via ang II.

The shift in sodium intake, a physiological modifier of the endogenous RAAS activity, affected adiponectin. The changes in circulating RAAS parameters, renin, aldosterone, and ang II, mirrored the changes in plasma adiponectin. This suggests that the influence of the RAAS on adiponectin is likely to be physiologically relevant and is not limited to pharmacological interventions. This holds all the more true because the range of sodium intake that we studied was not excessive and is well within the range encountered in the normal population (18). Our observations are in line with preliminary data, published in abstract form, showing a decrease in adiponectin concentration after 3 d of sodium restriction (19). It seems unlikely that an effect on renal elimination contributed to changes in circulating adiponectin in response to modification of sodium intake, because a HS was accompanied by an increase rather than by a decrease in GFR. To assess the possible clinical relevance of our findings, long-term studies in patients would be needed. We studied the effect of ACEi during HS, combining both physiological and pharmacological blockade of the RAAS. There was a small but significant increase in adiponectin during ACEi. This is in line with earlier data from others in type 2 diabetic and hypertensive patients (13, 20). However, this has not been shown previously in healthy subjects.

We found that exogenous ang II suppressed adiponectin, supporting a role for the RAAS in regulation of adiponectin in human. These data extend recent data in rats (14, 21). We found that the suppressor effect on adiponectin was present during both LS and HS and was already present at nonpressor doses of ang II. Because ang II elicited a pronounced drop in adiponectin even at the lowest dose used here, we were not able to identify a threshold dose. During both conditions, after 3 h of ang II infusion, the plasma adiponectin concentrations were approximately half of the baseline concentrations. The estimated half-life of adiponectin is 2.5 h (22). Taken together, these findings thus suggest that the release of adiponectin from adipocytes may to a considerable extent be blocked by ang II.

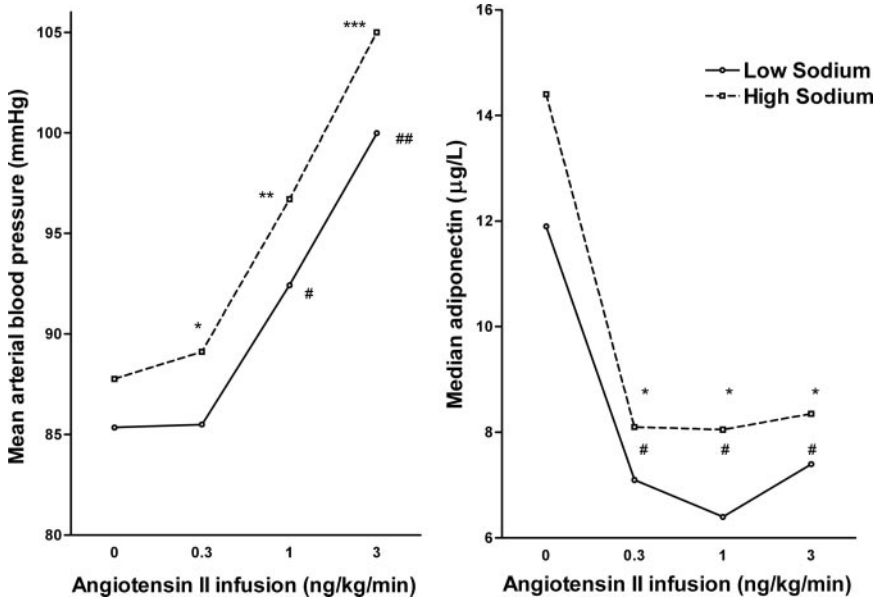

FIG. 2. MAP and median adiponectin concentrations during acute ang II infusion in healthy man. *Left*, Dose-dependent increase in MAP during ang II infusion during LS (*solid lines*) and HS (*dashed lines*) (mean values are given); *right*, decrease in adiponectin during ang II infusion during LS (*solid lines*) and HS (*dashed lines*) (median values are given). $P < 0.05$: *, LS *vs.* baseline; **, LS *vs.* baseline and 0.3 ang II ng/kg·min; ***, LS *vs.* baseline, 0.3, and 1 ang II ng/kg·min; #, HS *vs.* baseline; ##, HS *vs.* baseline and 0.3 ang II ng/kg·min. MAP was analyzed by Student's paired *t* test and adiponectin by Wilcoxon signed rank test.

Which mechanisms could be involved in the effects of ang II on adiponectin? Clasen *et al.* (23) showed that blockade of the ang II type I receptor can induce stimulation of adiponectin mRNA expression in adipocytes, suggesting that the ang II type I receptor is involved. Recent data from Kurata *et al.* (24) show that olmesartan, an ang II type 1 receptor blocker, attenuates hypoadiponectinemia consequent to obesity and aging in mice. This is in line with observations in rats by Ran *et al.* (14) who found decreased adiponectin concentrations during ang II infusion that were restored by the olmesartan. They observed changes in adiponectin concentrations after chronic infusion of ang II. However, we observed changes in adiponectin concentrations already after 1 h of infusion of ang II. The ang II type I receptor is expressed in adipocytes (25). Therefore, a possible mechanism could be that stimulation of the ang II type I receptor blocks the release of adiponectin from adipose tissue. However, we don't have direct proof of a role of the ang II type 1 receptor, because we did not study the effects of ang II infusion on adiponectin in combination with an angiotensin receptor type 1 blockade.

Analysis of the changes in adiponectin during ang II infusion in relation to sodium status reveals a parallel between the responses of blood pressure and adiponectin. The blood pressure response to ang II was increased during HS, which is in line with previous observations that HS potentiates the pressor response to ang II (26). The mechanism of the potentiation of the pressor response to ang II by HS is assumed to be both lower receptor occupancy as well as up-regulation of the ang II type I receptor (27). Interestingly, in our study, the response of adiponectin to exogenous ang II was enhanced by HS, which parallels the potentiation of the pressor response. Additional studies into the role of the ang II type I receptor in the regulation of adiponectin on local adipose tissue level (28) and the impact on plasma concentration are obviously warranted.

Another possible mechanism by which our results could

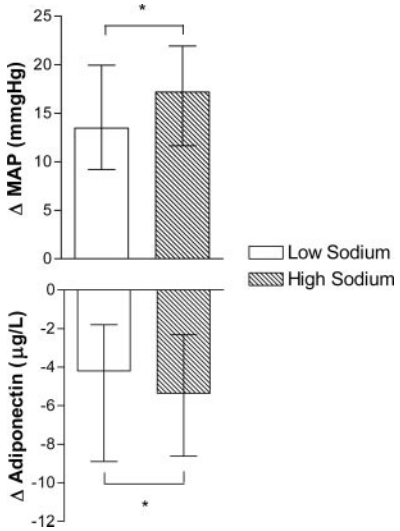

FIG. 3. Ang II-induced change in MAP and plasma adiponectin. *Top*, Change in MAP from baseline to 3 ng/kg·min. The blood pressure change is greater during a HS. The blood pressure sensitivity for ang II is modulated by sodium intake. *Bottom*, Change in adiponectin from baseline to 3 ng/kg·min. The adiponectin decrease during ang II infusion was higher during HS. Data are expressed as median (25th and 75th percentile). *, $P < 0.05$ for LS *vs.* HS.

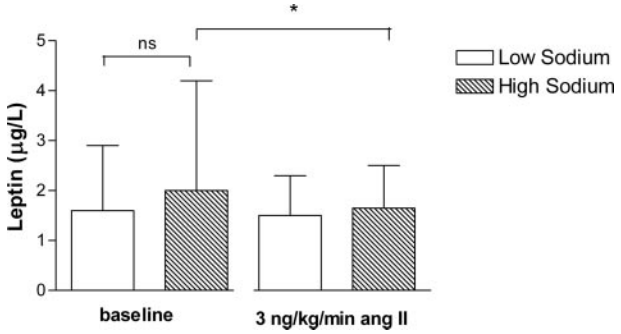

FIG. 4. Plasma leptin concentrations at baseline and during ang II infusion. Data are expressed as median (25th and 75th percentile). *, $P < 0.05$ for LS *vs.* HS (Wilcoxon signed rank test). ns, Not significant.

be explained is the sympathetic nervous system. It is known that both dietary sodium restriction and ang II infusion lead to an increased activity of the sympathetic nervous system activity (29, 30). Other studies have shown that β-adrenergic stimulation inhibits adiponectin gene expression (31). Moreover, Nowak *et al.* (32) show that central sympathetic blockade with rilmenidine increases adiponectin concentration. Further elucidation of the interrelationships between ang II, the sympathetic nervous system, and adiponectin are necessary.

What could be the implications of an effect of ang II on circulating adiponectin? Several studies reported increased insulin sensitivity on HS (33, 34), and our findings raise the possibility that effects on adiponectin may be involved. However, we did not find any changes in insulin and glucose concentrations or in the HOMA index, as a measure of insulin sensitivity, in response to HS. This lack of effect on parameters of glucose homeostasis could be attributable to the time span of HS as well as to the magnitude of changes in sodium balance elicited by our diet intervention. Therefore, these assumptions need further substantiation. Moreover, the antiinflammatory and vascular protective effects of adiponectin would provide an attractive additional mechanism to explain why RAAS blockade may exert therapeutic effects in conditions where the prior activity of the endogenous RAAS is low, *i.e.* during HS and volume excess.

To investigate whether plasma concentration of other adipokines were also affected by sodium intake and ang II infusion, we determined plasma leptin concentration at baseline and during the highest dose of ang II infusion. We observed a small increase of leptin during HS. However, this was not significant, albeit in the same direction as adiponectin. Previously, a moderate decrease of plasma leptin concentration by dietary sodium restriction has been described (35). During HS, ang II infusion induced a small but significant decrease in leptin. Compared with the changes of adiponectin during ang II infusion, the leptin changes were less pronounced (with ang II at 3 ng/kg·min, there was a 35% adiponectin decrease and 15% leptin decrease). Previous *in vitro* studies showed that ang II increases leptin secretion (36, 37). However, Cassis *et al.* (38) showed in rats that locally produced ang II directly increases leptin release from adipocytes but that chronic infusion of ang II in rats decreases plasma leptin concentrations. This study shows the complexity of studying adipokines, depending on the physiological and experimental setting used. Of note is that the leptin concentrations are very low, most probably related to our healthy population.

A possible limitation of our study is that we did not measure high molecular weight (HMW) adiponectin, which is assumed to be the active form of the protein (39). However, recently, Aso *et al.* (40) showed that there is very strong correlation ($r = 0.969$) between total adiponectin and HMW adiponectin concentrations in type 2 diabetic patients. Moreover, both total and HMW adiponectin concentrations are independent risk factors for the development of type 2 diabetes (39).

In summary, plasma adiponectin is inhibited during acute infusion of ang II in healthy men. Moreover, adiponectin increased during physiological suppression of the RAAS by HS. Thus, adiponectin may provide a link between the RAAS and metabolic status. Further elucidation of the interrelationships between ang II and adiponectin might provide a basis for better intervention in the cardiovascular complications of insulin-resistant states.

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