The Effects of Angiotensin-II on Lipolysis in Humans

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Adipocytes express many of the proteins of the renin-angiotensin system including angiotensinogen and AT_1-receptors. A principal function of adipocyte tissue is the provision of energy substrate through lipolysis. This study was undertaken to determine if angiotensin-II (Ang-II) infusion or blockade of the renin-angiotensin system by angiotensin-converting enzyme (ACE) inhibitor therapy with enalapril altered lipolytic activity and substrate oxidation. Eleven healthy male subjects were enrolled in the first study and postabsorptive whole-body lipolysis activity was measured using a stable isotope of glycerol ($^2H_5$-glycerol). Substrate oxidation was determined using indirect calorimetry in the Clinical Research Center. Subjects were then sequentially treated with low-dose Ang-II infusion (0.3 and then 1.0 ng/kg/min) on separate days, and the lipolysis and oxidation studies were repeated. Lastly, each subject was treated with 2 weeks of ACE inhibitor with enalapril (20 mg daily) and underwent lipolysis and oxidation studies for a fourth time. In a second study, 14 healthy male subjects were enrolled and underwent an identical baseline lipolysis and substrate oxidation assessment. These subjects then received an Ang-II infusion at pressor doses (10 ng/kg/min), and changes in lipolytic activity and substrate oxidation were measured again. In the first study, there was no effect on lipolysis activity from low-dose Ang-II infusion (baseline lipolysis activity (mean ± SD) 2.06 ± 0.55 μmol/kg/min, 2.10 ± 0.69 μmol/kg/min after 0.3 ng/kg/min, and 2.32 ± 0.56 μmol/kg/min after 1.0 ng/kg/min) or enalapril therapy (2.35 ± 1.00 μmol/kg/min). In the second study, the larger dose of Ang-II increased blood pressure by 14/17 mm Hg, but there was no effect on lipolysis activity (1.36 ± 0.49 μmol/kg/min *v* 1.63 ± 0.82 μmol/kg/min). Substrate oxidation rates were largely unaffected by Ang-II infusions or enalapril therapy. There was no evidence that treatment with subpressor or pressor dosages of Ang-II produced a significant alteration in lipolytic activity. Moreover, blockade of the renin-angiotensin system with enalapril was equally unremarkable in its effects on whole-body lipolysis. These data support the general concept that the renin-angiotensin system in adipocytes serves more to regulate the regional blood flow to adipose tissue and the size and number of fat cells rather than participating directly in the regulation of energy substrate.

THE RENIN-ANGIOTENSIN system regulates blood pressure and salt and water balance through well-described processes that revolve around the generation of angiotensin-II (Ang-II).[1] Ang-II causes vasoconstriction, reduces urine sodium excretion, stimulates aldosterone secretion, increases thirst, and augments sympathetic neural activity.[2] In the classical pathway of the renin-angiotensin system, the kidney is the major source of circulating renin activity, which generates angiotensin-I from the parent protein angiotensinogen. Circulating angiotensinogen is largely produced by the liver. Once angiotensinogen is cleaved to angiotensin-I, endothelium in the lung vasculature and elsewhere convert angiotensin-I to Ang-II. In the past 2 decades, several lines of research have provided evidence that there are also tissue renin-angiotensin systems, which function on a local level.[3] Among the tissues possessing a local renin-angiotensin system, adipocytes have been shown to possess several features of the renin-angiotensin system,[4,5] although the precise function of Ang-II in adipocyte metabolism, particularly with respect to lipolysis, is unclear.

Ang-II exerts virtually all of its significant clinical effects through the AT_1-receptor, and fat cells express AT_1-receptors on their surface.[6] However, it is not clear to what extent Ang-II, whether derived internally or generated remotely, influences fat cell metabolism. In particular, because lipolysis represents a principal adipocyte metabolic process, and because therapy with drugs, such as diuretics (which increase plasma renin activity), increase triglyceride concentrations,[7] perhaps through increasing fatty acid efflux by stimulation of adipocyte lipolysis, the hypothesis that Ang-II may influence lipolytic activity was generated. Consequently, this study was undertaken to evaluate the effects of Ang-II on lipolytic activity. Doses of Ang-II, which lack a blood pressure response as well as dosages that produce a significant blood pressure increase, were used. In addition, subjects also received the angiotensin-converting enzyme (ACE) inhibitor enalapril for 2 weeks to determine the effect of reduced Ang-II formation on lipolysis. Indirect calorimetry was performed on each subject to determine whether changes in lipolytic activity, if they occurred, would be accompanied by alterations in substrate (carbohydrate and lipid) oxidation.

MATERIALS AND METHODS

Subjects

Two protocols were used in this investigation. A total of 22 male subjects were recruited for these studies. Subjects were recruited by advertisement and word of mouth and were reimbursed a nominal sum for participation. All procedures were approved by the Institutional Review Board of The University of Texas Medical Branch, and each subject gave informed, written consent.

After enrollment, each subject underwent a standard history and physical examination. Laboratory evaluations included a complete biochemical profile. Each subject underwent a 3-hour oral glucose tolerance test (OGTT). A Diabetic OGTT, as determined by the National Diabetes Cooperative Group recommendations on oral glucose tolerance testin,[8] resulted in exclusion from participation.

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A

FIRST STUDY							
			Low Dose Ang-II Infusion			Enalapril 20 mg/day	
Time	Baseline	(2 weeks)	0.3 ng/kg/min	1 ng/kg/min	(1 week)	(2 weeks)	Enalapril
0600h-0900h			Ang-II infusion	Ang-II infusion			
0700h-0900h	$^2H_5$-glycerol		$^2H_5$-glycerol	$^2H_5$-glycerol			$^2H_5$-glycerol
0800h,0900h	Calorimetry		Calorimetry	Calorimetry			Calorimetry
			(Consecutive days)				

B

SECOND STUDY			
		Pressor Dose Ang-II Infusion	
Time	Baseline	(Next day)	10 ng/kg/min
0600h-0900h			Ang-II infusion
0700h-0900h	$^2H_5$-glycerol		$^2H_5$-glycerol
0800h,0900h	Calorimetry		Calorimetry

Fig 1. (A) Sequence of events in the first study; (B) sequence of events in the second study.

First Study

In this first study, subjects were first evaluated in the postabsorptive state, followed 2 weeks later by repeat studies while receiving 2 subpressor doses (0.3 and 1.0 ng/kg/min) of Ang-II, and finally 3 weeks after that after 2 weeks of enalapril therapy administered as 10 mg twice a day, including the final morning of study. Figure 1 diagrams the sequence in the first and second studies. Subject participation lasted a total of about 5 weeks. Subjects were admitted to the General Clinical Research Center (GCRC) at 5:00 to 6:00 PM the evening before the study. A 12-hour urine sample for urea nitrogen excretion was collected from 6:00 PM through 6:00AM. In both studies (this first 1 and the second), the studies were performed in the sequences outlined, as each period of isotopic equilibrium was followed by a euglycemic clamp, the results of which have been previously published.[9,10] The protocol sequence of studies was based on the euglycemic clamp investigations.

On arrival, each subject was given a standard meal at 5:30 to 6:00 PM. After 6:00 PM, only water was allowed. At 6:00 AM on the morning of each study, intravenous catheters were inserted in each arm. One catheter was placed in the hand or wrist and warmed to 55 to 60°C (to "arterialize" the blood[11]), and all blood samples were withdrawn from this catheter. The other catheter was placed in the opposite forearm and used for all infusions. The subjects were at rest for approximately 1 hour before isotope infusion studies were initiated. In the baseline study, beginning at 7:00 AM, a primed infusion of $^2H_5$-glycerol (with a priming dose 2.2 μmol/kg bolus over 30 to 40 seconds) was given, followed by a constant infusion (0.11 μg/kg/min). Use of this rate of isotope infusion in prior studies achieves isotopic equilibrium at about 90 minutes and plasma enrichment (in both the first and second study) with $^2H_5$-glycerol of approximately 4%. After 105 minutes, plasma was sampled from the warmed hand for $^2H_5$-glycerol isotopic enrichment and plasma unesterified fatty acid concentrations at 5-minute intervals (total of 4 samples over 15 minutes). The 4 determinations of glycerol enrichments were averaged to determine the whole-body lipolytic rate.[12,13] Plasma catecholamines and plasma insulin concentrations were obtained after 1 and 2 hours of $^2H_5$-glycerol infusion. A supine plasma renin activity was obtained at 8:00 AM following 1 hour of $^2H_5$-glycerol infusion in the baseline study and during the study performed after 2 weeks of enalapril therapy (see below). Indirect calorimetry was performed at the end of the first and the second hour of $^2H_5$-glycerol infusion, and substrate oxidation rates were derived using standard formula[14] on the averaged readings. After study completion, subjects were discharged from the CRC and returned 2 weeks later for consecutive studies over 48 hours, performed in an identical fashion, except that subjects received an intravenous infusion of Ang-II (0.3 ng/kg/min on the first day and 1.0 ng/kg/min on the second day), which began right after intravenous catheter placement so that the $^2H_5$-glycerol infusion and calorimetry determinations were still performed between 7:00 to 9:00 AM. Blood pressure and heart rate were monitored at 10-minute intervals throughout the Ang-II infusion using a Dinamap automated blood pressure monitor (Critikon, Tampa, FL). No plasma renin activity sampling was performed during the Ang-II infusion studies. Subjects returned for a final study 3 weeks later during the last 2 weeks of which enalapril therapy was given as 10 mg twice a day. The study was repeated (with renin sampling), and all subjects received a dose of enalapril at 6:00 AM to ensure continued ACE inhibition. Renin sampling was performed show blockade of the renin-angiotensin system with enalapril.

Second Study

In the second study, 14 subjects were recruited for 2 studies, identical to the procedures outlined previously, performed on 2 consecutive days. Three of these subjects participated in the first study 1 year before enrolling in the second study. Seven subjects underwent a baseline study on the first day, with a pressor dose infusion of Ang-II (10 ng/kg/min) on the second day. Seven subjects underwent the pressor dose infusion of Ang-II on the first day, followed by the baseline study on the second day. As with the first study, Ang-II infusions were begun shortly after intravenous catheter placement so that lipolytic determinations and indirect calorimetry were performed between 7:00 to 9:00 AM. Blood pressure and heart rate were monitored at 10-minute intervals throughout the Ang-II infusion using an automated blood pressure monitor. No subject required discontinuation of Ang-II infusion for safety purposes.

Analyses

Plasma catecholamine levels were determined by radioenzymatic assay. Normal range for supine plasma norepinephrine is 200 to 400 pg/mL. Plasma insulin levels were determined by radioimmunoassay (INCSTAR, Stillwater, MI). Plasma glycerol concentrations were measured with an AutoAnalyzer (Bayer-Technicon, Tarrytown, NY). Enrichment of plasma with $^2H_5$-glycerol was determined by gas chromatography/mass spectroscopy using an MSD 5971 system (Hewlett Packard, Palo Alto, CA) with an HP-1 12 $\times$ 0.2 mm fused silica capillary column after formation of the trimethyl-silyl derivative.[15] The rate of appearance of glycerol (Ra glycerol) was determined using the

Steele equation for steady state isotope kinetics.[16] Plasma fatty acids were determined using gas chromatography. Plasma renin activity was determined using the method of Sealey and Laragh.[17]

Data

All data are expressed as mean ± SD. Data in the first study were compared using a repeated measures analysis of variance (ANOVA) (Sigmastat; Jandel Scientific, San Rafael, CA) with post hoc comparisons performed using Tukey's test. If data failed normal distribution testing, a repeated measures ANOVA on ranks was performed. Data in the second study were evaluated using a paired *t* test. A *P* value less than .05 was considered significant.

RESULTS

The demographic characteristics of the subjects are shown in Table 1.

In the first study, basal postabsorptive whole-body lipolytic rates were compared with lipolytic rates after 0.3 ng/kg/min and 1.0 ng/kg/min of Ang-II and then after 2 weeks of therapy with the ACE inhibitor therapy. Figure 2A shows the whole body lipolysis rate (represented by the Ra glycerol), plasma-free fatty acid concentration, plasma insulin concentration, and plasma norepinephrine concentrations. There were no statistically significant differences between the baseline control, the subpressor Ang-II infusions, or the enalapril therapy.

In the second study, the same data are plotted on Fig 2B. There were no statistically significant differences between the control baseline studies and the use of pressor doses of Ang-II.

In the first study, the plasma renin activity at 8:00 AM during the basal infusion was 1.0 ± 0.2 ng/mL/h compared with 12.1 ± 3.1 ng/mL/h after enalapril therapy ($P < .01$), indicating significant blockade of renin-angiotensin system was achieved.

There were no increases in blood pressure during the subpressor doses of angiotensin infusion. With the larger dose of angiotensin (10 ng/kg/min), the supine systolic blood pressure increased from 127 ± 3 mm Hg to 141 ± 4 mm Hg. The supine diastolic pressure increased from 72 ± 2 mm Hg to 89 ± 2 mm Hg.

Resting energy expenditure and substrate oxidation data after 2 hours of $^2H_5$-glycerol infusion are presented in Table 2. In the second study, the calorimetry data in 1 subject were not be obtained due to technical difficulties with the calorimeter. In general, differences in substrate oxidation and resting energy expenditure between the treatments were small and not clinically significant. The carbohydrate oxidation during the 1 ng/kg/min infusion of Ang-II was significantly higher than during the basal, 0.3 ng/kg/min, or enalapril regimens during the first study (Table 2). As shown in Fig 2A, the plasma fatty acid concentrations tended to be lower during the 1 ng/kg/min Ang-II infusion ($P = .056$), but this was not due to a difference in whole-body lipolytic rate, or was a reduction of plasma fatty acid concentration evident during the higher (10 ng/kg/min) dose infusion of Ang-II in the second study (Fig 2B).

Table 1. Demographics of Subjects

First study (n = 11)	
Age (yr)	25 ± 6
BMI (kg/m^2)	22.8 ± 2.7
Glucose (mg/dL)	100 ± 12
Second study (n = 14)	
Age (yr)	29 ± 9
BMI (kg/m^2)	23.2 ± 2.7
Glucose (mg/dL)	92 ± 10

Abbreviation: BMI, body mass index.

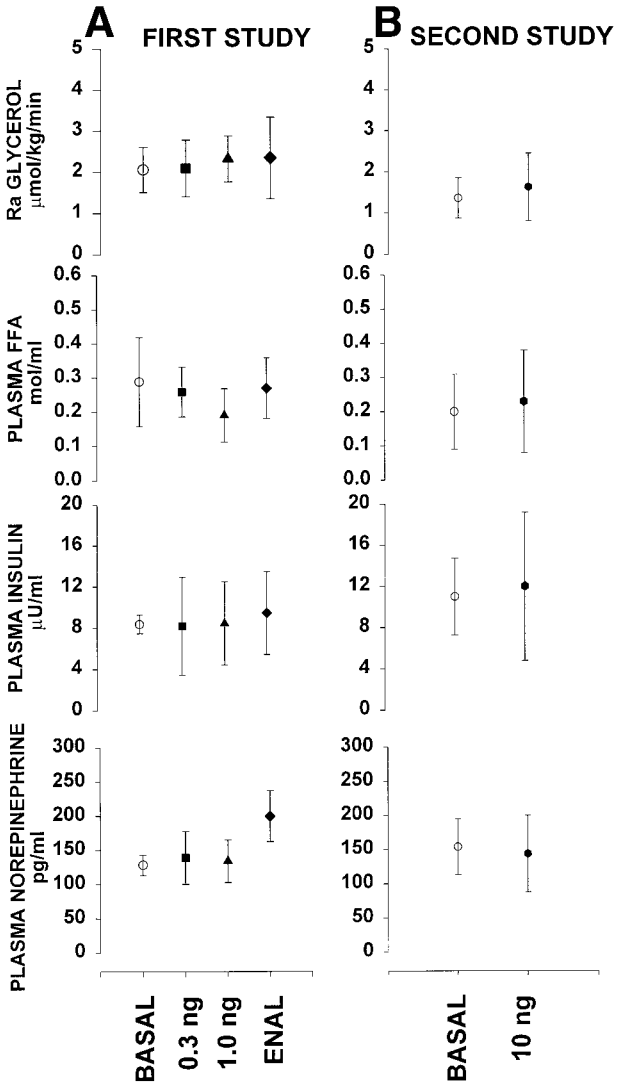

Fig 2. (A) Whole body lipolysis rate (represented by Ra glycerol) (top panel), plasma-free fatty acid concentration (upper middle panel), plasma insulin concentration (lower middle panel), and plasma norepinephrine concentrations (bottom panel). First study: ○, indicates basal condition; ■, Ang-II infusion at 0.3 ng/kg/min; ▲, Ang-II infusion at 1.0 ng/kg/min; ◆, enalapril therapy 20 mg daily for 2 weeks prior. (B) Second study: ○, basal condition; ●, Ang-II infusion at 10 ng/kg/min. Data shown are mean ± SD.

DISCUSSION

The data show no effect of an Ang-II infusion on basal whole-body lipolytic rates or plasma fatty acid concentrations, whether given in subpressor concentrations or in dosages that increase blood pressure. In addition, interruption of the renin-angiotensin system with the use of the ACE inhibitor, enalapril,

Table 2. Resting Energy and Substrate Utilization in Postabsorptive State

	Basal	0.3 ng/kg/min	1.0 ng/kg/min	Enalapril
First study				
Resting energy expenditure (kcal/kg/h)	23.6 ± 2.1	21.9 ± 2.3	23.1 ± 1.7	20.8 ± 2.9*
Carbohydrate oxidation (mg/kg/min)	1.3 ± 0.8	1.4 ± 0.8	2.4 ± 0.6†	1.3 ± 0.6
Lipid oxidation (mg/kg/min)	0.92 ± 0.33	0.75 ± 0.37	0.48 ± 0.31†	0.66 ± 0.28
Second study (n = 13, data absent on 1 subject)				
	Basal	10 ng		
Resting energy expenditure (kcal/kg/h)	24.2 ± 0.9	25.1 ± 0.8		
Carbohydrate oxidation (mg/kg/min)	1.8 ± 0.2	2.1 ± 0.2		
Lipid oxidation (mg/kg/min)	0.75 ± 0.09	0.72 ± 0.11		

*$P < .05$ compared with basal.

†$P < .05$ compared with basal, 0.3 ng/kg/min and enalapril.

was not associated with detectable alteration in whole-body lipolytic activity. The changes in substrate metabolism during the different treatment periods were small and limited to a statistically significant increase in glucose oxidation with a commensurate decrease in lipid oxidation during the 1 ng/kg/min Ang-II infusion and a small, but statistically significant, decrease in resting energy expenditure after the enalapril treatment. The absence of significant changes in insulin or catecholamines, primary regulators of lipolytic activity, are also consistent with a lack of effect of Ang-II on lipolysis in the doses used in this study.

Mammalian fat cells possess the messenger-RNA for angiotensinogen and express the angiotensinogen protein.[4,5] Thus, the active moiety of the renin-angiotensin system (Ang-II) is potentially available at the level of the adipopcyte. Human fat cells express the AT_1-receptor,[6] the principal receptor through which the clinical actions of Ang-II are mediated. In adipocytes, increases in intracellular calcium accompany increases in lipolysis.[11] Typically, when the AT_1-receptor is stimulated by Ang-II, activation of G proteins leads to stimulation of phospholipase C resulting in an increase in inositol-1,4,5 triphosphate (IP3) and diacyglycerol. IP3 generation results in an increase in cellular calcium concentration.[18] Thus, it was hypothesized that Ang-II stimulation of adipocytes could also increase lipolysis. However, no changes in whole-body lipolytic activity were detected in the current study despite these previous findings. The observations in the current study were interpreted as indicating that stimulation of the Ang-II receptors in adipocytes serves a function other than lipolytic regulation.

Alterations in nutritional status regulate the release of angiotensinogen from fat cells in rodents. Starvation reduces adipocyte angiotensinogen release, while feeding nearly doubles the angiotensinogen release compared with control conditions.[19] Increased angiotensinogen output increases the available substrate for Ang-II production. This was reasoned to occur as a means to regulate blood flow through adipose tissue during fasting and feeding. In this hypothesis, adipose tissue blood flow would increase during fasting (from less vasoconstriction resulting from less local angiotensinogen production) and blood flow would decrease during feeding (from more vasoconstriction resulting from more angiotensinogen production) to expedite fatty acid availability for fuel during fasting and limit fatty acid egress during feeding. On the other hand, Ang-II binding to adipocyte AT_1-receptors in vitro stimulates the production of prostacyclin.[20] Prostacyclin is vasodilatory and serves as a local mediator of increased blood flow. Prostacyclin also regulates adipocyte cell differentiation[21] and stimulates hyperplasia in adipocytes.[22] Thus, stimulation of the AT_1-receptor in adipocytes by Ang-II with subsequent prostacyclin release may facilitate the expansion of the fat cell mass through mechanisms, which increase blood supply and promote adipocyte growth. The ability of fat cells to promote angiogenesis in a manner that is preventable by prostaglandin blockade with indomethacin further supports this.[23]

A stable isotopic tracer of glycerol was used to measure lipolysis in this study. Isotopic tracers of glycerol are felt to be superior to using other aspects of the lipolytic pathway (such as unlabelled fatty acids).[12] Because the tracer was infused systemically, the lipolytic rate measured is whole-body and not limited to adipose tissue. Consequently, it is not possible to differentiate effects on adipose tissue from other tissues possessing lipolytic capacity such as skeletal muscle. However, the contribution of these other tissues in postabsorptive, normal weight, healthy individuals is likely to be small, and it is probable that these data represent predominantly the adipocyte contribution to whole-body lipolysis.

The changes noted during calorimetry were generally consistent with the absence of change in lipolytic activity. However, at the 1 ng/kg/min Ang-II infusion, glucose oxidation was higher, and lipid oxidation lower compared with baseline, Ang-II at 0.3 ng/kg/min, and the enalapril treatment in the first study, without a detectable change in energy expenditure during this dose of Ang-II infusion. Possibly, at the 1 ng/kg/min dose, a small increase in glycogenolysis by Ang-II[24] and a reciprocal increase in re-esterification within fat cells (neither

of which was measured in this study) occurred providing more glucose for substrate oxidation and reducing the flux of fatty acid into the circulation. The differences in resting energy expenditure after enalapril therapy were only significantly different when compared with the baseline study. No explanation for this was apparent from the data obtained in the first study. There was no effect on plasma insulin concentrations during any of the conditions in the first or second study, and the insulin-stimulated glucose uptake during a euglycemic clamp was unaffected by either lower dose of Ang-II or enalapril in the first study.[9] The pressor doses of Ang-II infusion given in the second study increased glucose uptake during the euglycemic clamp study, which followed the baseline isotope infusion period through an effect on skeletal muscle blood flow.[10]

Because a total of only 11 subjects in the first study and 14 in the second study were investigated in this study, it is possible that the power behind the study is inadequate to have detected a significant difference in lipolytic rate. It is also possible that a longer period of angiotensin infusion could possibly bring out differences in lipolytic activity not evident within the approximately 3 hours of infusion used in this investigation.

In summary, although adipocytes possess many aspects of the renin-angiotensin system including the expression of AT_1-receptors, there was no evidence in this study that stimulation of these AT1-receptors with subpressor or pressor dosages of Ang-II produces a significant alteration in lipolytic activity. Moreover, blockade of the renin-angiotensin system with enalapril was equally unremarkable in its effects on whole-body lipolysis. These data support the general concept that the renin-angiotensin system in adipocytes serves more to regulate the regional blood flow to adipose tissue and the size and number of fat cells rather than participating directly in the regulation of energy substrate.

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