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ANG II infusion promotes abdominal aortic aneurysms independent of increased blood pressure in hypercholesterolemic mice

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Cassis LA, Gupte M, Thayer S, Zhang X, Charnigo R, Howatt DA, Rateri DL, Daugherty A. ANG II infusion promotes abdominal aortic aneurysms independent of increased blood pressure in hypercholesterolemic mice. *Am J Physiol Heart Circ Physiol* 296: H1660–H1665, 2009. First published February 27, 2009; doi:10.1152/ajpheart.00028.2009.—Infusion of ANG II in hyperlipidemic mice augments atherosclerosis and causes formation of abdominal aortic aneurysms (AAAs). The purpose of this study was to define the contribution of ANG II-induced hypertension to these vascular pathologies. Male apolipoprotein E (apoE)- and LDL receptor (LDLR)-deficient mice were infused with ANG II (1,000 ng·kg⁻¹·min⁻¹) or norepinephrine (NE; 5.6 mg·kg⁻¹·day⁻¹) for 28 days. Infusion of ANG II or NE increased mean arterial pressure (MAP; ANG II, 133 ± 2.8; NE, 129 ± 13 mmHg) to a similar extent compared with baseline blood pressures (MAP, 107 ± 2 mmHg). Abdominal aortic width increased in both apoE-deficient (apoE^{-/-}) or LDLR-deficient (LDLR^{-/-}) mice infused with ANG II (apoE^{-/-}: 1.4 ± 0.1; LDLR^{-/-}: 1.6 ± 0.2 mm). In contrast, NE did not change diameters of abdominal aortas (apoE^{-/-}: 0.91 ± 0.03; LDLR^{-/-}: 0.87 ± 0.02 mm). Similarly, atherosclerotic lesions in aortic arches were much greater in mice infused with ANG II compared with NE. At a subpressor infusion rate of ANG II (500 ng·kg⁻¹·min⁻¹), AAAs developed in 50% of apoE^{-/-} mice. Alternatively, administration of hydralazine (250 mg/l) to ANG II-infused apoE^{-/-} mice (1,000 ng·kg⁻¹·min⁻¹) lowered systolic blood pressure (day 28: ANG II, 157 ± 6; ANG II/hydralazine, 135 ± 6 mmHg) but did not prevent AAA formation or atherosclerosis. These results demonstrate that infusion of ANG II to hyperlipidemic mice induces AAAs and augments atherosclerosis independent of increased blood pressure.

aneurysms; hypertension; vascular lesions

ANG II EXERTS SEVERAL EFFECTS to increase blood pressure, including vasoconstriction, heightened sympathetic nervous system activity, and secretion of aldosterone (29). In addition to these well-described effects on blood pressure, it is becoming increasingly evident that the renin-angiotensin system contributes to the development of other vascular diseases, including atherosclerosis and abdominal aortic aneurysms (AAAs) (9, 25). Several lines of evidence have demonstrated that ANG II does not promote atherosclerosis through an indirect effect of increased blood pressure (25). This evidence includes the contrasting effects of chronic infusion of ANG II and norepinephrine (NE) on atherosclerosis in apoE^{-/-} mice (33). Also, lesions size was increased to a greater extent in apoE^{-/-} mice with renin-dependent hypertension from two-

kidney, one-clip surgery compared with non-renin-dependent hypertension induced by one-kidney, one-clip surgery (20).

In contrast to the well-characterized independence of blood pressure on ANG II-induced atherosclerosis (33), the contribution of pressure per se to the development of ANG II-induced AAAs has not been defined. This is important since ANG II-induced atherosclerosis and AAAs are distinct vascular pathologies with disparate mechanisms (31). AAAs formed from infusion of ANG II are characterized by a large luminal expansion due to disrupted medial elastin within the first 10 days of infusion (32). This is followed by a phase of tissue remodeling characterized by the presence of extracellular matrix fragmentation, accumulation of macrophages, and B and T lymphocytes, and progressive lumen expansion (2, 31). In contrast, infusion of ANG II augments developing atherosclerotic lesions on the intimal surface in a manner similar to hypercholesterolemia-induced atherosclerosis (12). These findings suggest distinct cell targets and mediators of ANG II to induce atherosclerosis and AAA formation.

Hypertension has been suggested as an unrelated or weak risk factor for AAA development (23). However, assessment of correlations between blood pressure and AAA development is complicated by the definition of hypertension (based on treatment for the condition). Also, antihypertensive drugs may influence the development of AAAs independent of their blood pressure-lowering effects. At infusion doses typically employed to induce AAAs in hyperlipidemic mice, the ANG II model of AAAs exhibits both hypercholesterolemia and hypertension, making it a suitable model to address the distinct contribution of these variables to AAA formation. The purpose of this study was to define the contribution of ANG II-induced increases in blood pressure to AAA formation. This was accomplished by contrasting the effects of infusions of either ANG II or NE at rates that elevated blood pressure to a similar extent in the two most commonly used strains of mice for AAA studies [apolipoprotein E-deficient (apoE^{-/-}) and low density lipoprotein receptor-deficient (LDLR^{-/-}) mice (7, 10)]. As a second approach, we defined effects of subpressor infusion rates of ANG II to apoE^{-/-} mice on AAA formation. Finally, we determined the effects of attenuating ANG II-induced blood pressure increases by the concomitant infusion of hydralazine. These studies demonstrated that blood pressure per se is not a major determinant of ANG II-induced AAAs.

METHODS

Animals and Drug Infusions

Male LDLR^{-/-} and apoE^{-/-} mice (2 mo of age; backcrossed 10 times on a C57BL/6 background) were originally obtained from the Jackson Laboratory (Bar Harbor, ME) and maintained at the Univer-

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sity of Kentucky. ApoE^{-/-} mice were fed a standard diet and provided water ad libitum. LDLr^{-/-} mice were fed a diet supplemented with saturated fat (milk fat; 21% wt/wt) and cholesterol (0.15%; wt/wt, catalog no. TD88137; Harlan Teklad) for 1 wk before, and 4 wk during, ANG II infusion. Both apoE^{-/-} and LDLr^{-/-} mice were infused with either ANG II (1,000 ng·kg⁻¹·min⁻¹; n = 26) or NE (5.6 mg·kg⁻¹·day⁻¹; n = 26) by osmotic minipump (model 2004; Durect) for 28 days. Other studies examined effects of subpressor infusion rates of ANG II (500 ng·kg⁻¹·min⁻¹; n = 5) or saline (n = 5) to male apoE^{-/-} mice for 28 days. To lower blood pressure, male apoE^{-/-} mice were administered hydralazine in the drinking water (250 mg/l) for 1 wk before, and throughout, infusion of ANG II (1,000 ng·kg⁻¹·min⁻¹ for 28 days; n = 12/group, control vs. hydralazine). All experiments involving mice conform to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Kentucky Institutional Animal Care and Use Committee.

Measurement of Blood Pressure

Telemetry. Mice (male, apoE^{-/-}, 2 mo of age) were infused with either ANG II (1,000 ng·kg⁻¹·min⁻¹) or NE (5.6 mg·kg⁻¹·day⁻¹; n = 6/group). Mice were anesthetized with isoflurane, and left carotid arteries were isolated. Telemeter catheters were inserted in arteries and advanced to reach aortic arches. Telemetry implants (model TA11PA-C10; Data Sciences International, St. Paul, MN) were placed in a subcutaneous pocket on the right flank. Mice were allowed to recover for 1 wk before obtaining baseline measurements of blood pressure (3 consecutive days at 24 h/day). Twenty-four-hour measurement of blood pressure was then acquired on day 16 of infusions. This time point was chosen as the longest duration of infusion for which all catheters were patent. The telemeter signal was processed using a model RPC-1 receiver, a 20-channel data-exchange matrix, APR-1 ambient pressure monitor, and a Dataquest ART 2.3 acquisition system (Data Sciences International). The system was programmed to acquire data for 10 s every minute and to calculate 10-min means of the mean, systolic, and diastolic blood pressure.

Volume pressure recording. Systolic blood pressure was measured by volume pressure recording of the tail using the CODA noninvasive blood pressure system on five consecutive days (Kent Scientific, Torrington, CT).

Atherosclerosis and AAA quantification. Atherosclerosis was quantified as lesion areas on the intimal surface of aortic arches, as described previously (13). Because carotid catheters may influence intimal lesion formation, atherosclerosis was not quantified in apoE^{-/-} mice that were implanted with radiotelemetry devices. AAAs were quantified in vivo by measurement of maximal lumen diameters of suprarenal abdominal aortas using high-frequency ultrasound on anesthetized mice (ketamine/xylazine, 100/10 mg/kg, respectively, ip on day 0 and day 28) (2). AAAs were also quantified ex vivo by measurement of maximal width of suprarenal aortas dissected free from mice at 28 days and with extraneous tissues removed.

Measurement of plasma components. At study endpoint, blood was obtained from anesthetized mice (ketamine/xylazine 100/10 mg/kg ip) by left ventricular puncture in tubes containing EDTA (0.05 M).

Plasma was obtained by centrifugation (5,000 rpm) at 4°C for 10 min. Plasma renin concentrations were measured by incubating (37°C, 30 min) mouse plasma (8 μl) with an excess of partially purified rat angiotensinogen in phosphate buffer (pH 7.0) containing EDTA (0.05 M) and enalapril (10 μM) for generation of ANG I, followed by RIA (6, 12). Total serum cholesterol concentrations were measured as described previously (25).

Statistics. To compare two groups on a continuous response variable, we used a two-sample Student's *t*-test with data being verified that it was within the constraints of this test. To compare more than two groups on a continuous response variable, we used one or two-way ANOVA followed by Bonferroni's post hoc analysis. Percent incidence of AAAs was analyzed by Fisher's exact test. *P* values <0.05 were considered to be statistically significant. Differences that attained statistical significance are represented in Tables 1 and 2 and Figs. 1–4. All data are represented as means ± SE.

RESULTS

Infusions of ANG II and NE Promote Similar Increases in Blood Pressure but Have Disparate Effects on AAAs and Atherosclerosis

Infusions of either ANG II or NE had no effect on body weight or total serum cholesterol concentrations in either apoE^{-/-} or LDLr^{-/-} mice (Table 1). Plasma renin concentrations were greater in LDLr^{-/-} mice than apoE^{-/-} mice, regardless of drug infusions (Table 1). Because LDLr^{-/-} and apoE^{-/-} mice are both on a C57BL/6 background, the addition of the high-fat diet to LDLr^{-/-} mice to induce hypercholesterolemia may have contributed to higher plasma renin concentrations in LDLr^{-/-} compared with apoE^{-/-} mice. In agreement with previous results demonstrating that infusion of ANG II results in negative feedback inhibition of kidney-derived renin (6, 18), plasma renin concentrations were lower in mice infused with ANG II compared with NE. In apoE^{-/-} mice infused with ANG II or NE, systolic, diastolic, and mean arterial pressure increased within 1 day of infusion and were elevated for 16 days [Fig. 1A and Supplemental Table 1 (Supplemental data for this article can be found on the *American Journal of Physiology: Heart and Circulatory Physiology* website)]. In addition, mice infused with ANG II exhibited similar blood pressure elevations to those infused with NE. Heart rate and pulse pressures were not different in apoE^{-/-} mice infused with ANG II or NE (Supplemental Table 1). In LDLr^{-/-} mice infused with either ANG II or NE, systolic blood pressures were also indistinguishable (155 ± 6 vs. 166 ± 5 mmHg, respectively).

Noninvasive detection of aortic dimensions by high-frequency ultrasound demonstrated that 28 days of ANG II infusion in apoE^{-/-} and LDLr^{-/-} mice resulted in increased lumen diameters of suprarenal abdominal aortas compared with measurements before infusion (Fig. 1B). In contrast, NE

Table 1. Characteristics of apoE^{-/-} and LDLr^{-/-} mice infused with either NE or ANG II

	NE		ANG II	
	LDLr ^{-/-}	ApoE ^{-/-}	LDLr ^{-/-}	ApoE ^{-/-}
Body wt, g	28.5 ± 0.4	28.1 ± 0.3	28.1 ± 0.5	27.8 ± 0.4
Serum cholesterol concentration, mg/dl	1,262 ± 102	368 ± 25*	1,403 ± 74	437 ± 49*
Plasma renin concentration, ng/ml	5.79 ± 0.78	3.56 ± 0.61*	1.55 ± 0.30†	0.86 ± 0.07*†

Data are means ± SE from n = 26 mice/group. NE, norepinephrine; LDLr^{-/-}, low density lipoprotein receptor deficient; ApoE^{-/-}, apolipoprotein E deficient. *P* < 0.05, significantly different from LDLr^{-/-} within infusions (*) and significantly different from NE within strains (†).

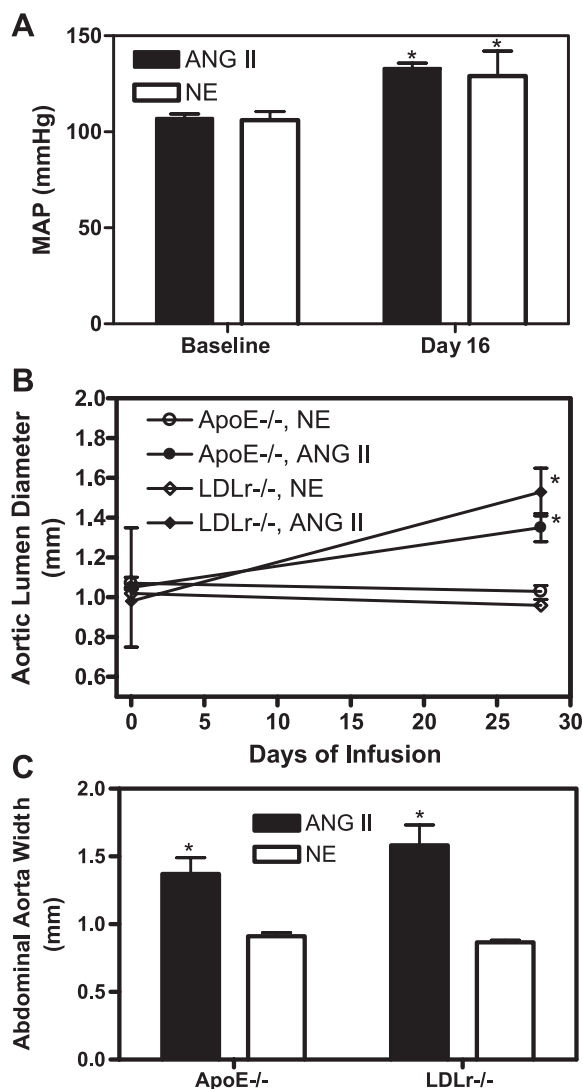


Fig. 1. Infusions of either ANG II or norepinephrine (NE) increase mean arterial pressure (MAP), but only ANG II promotes abdominal aortic aneurysm (AAA) formation. *A*: MAP was increased to a similar extent by infusions of either ANG II or NE. *B*: aortic lumen diameters were increased by infusions of ANG II in apoE^{-/-} or LDLr^{-/-} mice compared with measurements before infusion. In contrast, infusions of NE did not change baseline aortic lumen diameters. *C*: external diameter (maximal width) of suprarenal abdominal aortas from apolipoprotein E-deficient (apoE^{-/-}) or low density lipoprotein receptor-deficient (LDLr^{-/-}) mice infused with either saline or ANG II. Data are means \pm SE from $n = 6$ mice/group (*A*) or $n = 26$ mice/group/treatment (*B* and *C*). *Significantly different from baseline (*A*), from baseline (0) and NE (*B*), or from NE (*C*).

infusion in apoE^{-/-} and LDLr^{-/-} mice did not increase lumen diameter (Fig. 1*B*) or promote aneurysmal pathology [Supplemental Fig. 1 (Supplemental material for this article can be found on the *American Journal of Physiology: Heart and Circulatory Physiology* website.)]. AAA incidence was similar in apoE^{-/-} and LDLr^{-/-} infused with ANG II (53 and 47%, respectively), but no AAAs formed in mice infused with NE (Supplemental Fig. 1). Measurements of excised aortas demonstrated that maximal width of suprarenal abdominal aortas were increased in both apoE^{-/-} and LDLr^{-/-} mice infused with ANG II, but not in mice infused with NE (Fig. 1*C*). In agreement with many studies, infusion of ANG II increased the

aortic intima areas of atherosclerosis. In accord with the findings of Weiss et al. (33), NE infusions in these mice promote a lesser increase in atherosclerosis area (Fig. 2).

Infusion of Subpressor Doses of ANG II Promote AAA Formation

Infusion of ANG II at 500 ng·kg⁻¹·min⁻¹ to apoE^{-/-} mice did not influence body weight (saline, 26.3 \pm 1.3; ANG II, 24.9 \pm 1.3 g). Systolic blood pressure was not significantly different in mice infused with saline compared with ANG II (saline, 117 \pm 2; ANG II, 130 \pm 6 mmHg, $P = 0.08$). Aortic lumen diameters were increased compared with measurements before infusion in mice infused with ANG II, but not saline (Fig. 3), resulting in a 50% AAA incidence.

Attenuation of ANG II-Induced Increases in Blood Pressure did not Influence Development of Atherosclerosis or AAA Formation

Hydralazine administration during ANG II infusion had no effect on body weight, serum cholesterol concentrations, or plasma renin concentrations in apoE^{-/-} mice infused with ANG II (Table 2). Before infusions of ANG II, systolic blood pressures were not different in apoE^{-/-} mice administered hydralazine compared with vehicle (Fig. 4). Infusion of ANG II increased systolic blood pressure over baseline in mice administered vehicle or hydralazine. However, systolic blood pressures were greater in ANG II-infused apoE^{-/-} mice administered vehicle compared with hydralazine.

Abdominal aortic lumen diameters on day 28 of ANG II infusion were not significantly different in apoE^{-/-} mice administered hydralazine compared with vehicle (1.59 \pm 0.21 vs. 1.38 \pm 0.03, respectively). AAA incidence was also not significantly different in ANG II-infused mice administered hydralazine or vehicle (58 vs. 50%, respectively). Finally, atherosclerotic lesion areas were not influenced significantly by administration of hydralazine to ANG II-infused mice (hydralazine: 3.00 \pm 0.40; vehicle: 1.74 \pm 0.50 mm²; $P = 0.06$).

DISCUSSION

This study demonstrated that AAA formation resulting from infusion of ANG II to hypercholesterolemic mice occurs independent of blood pressure-elevating effects of this octapeptide.

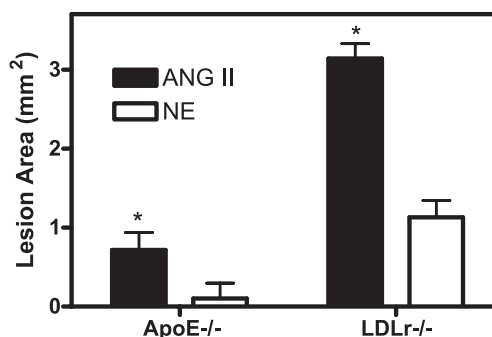


Fig. 2. Atherosclerotic lesions were increased to a greater extent by infusion of ANG II ($n = 26$ /genotype) compared with NE ($n = 26$ /genotype) in both apoE^{-/-} and LDLr^{-/-} mice. Lesion areas were greater in LDLr^{-/-} compared with apoE^{-/-} mice, regardless of drug infusions. Lesion areas were greater in mice infused with ANG II compared with NE, regardless of genotype. Data are means \pm SE on right. *Significantly different from NE, $P < 0.05$.

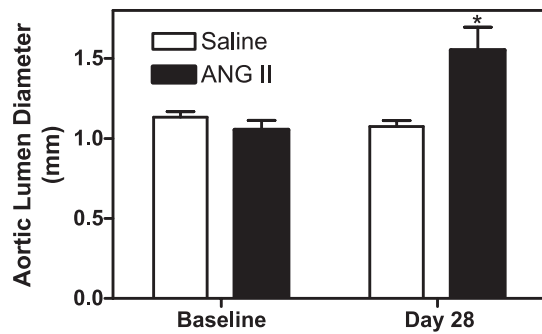


Fig. 3. Infusion of a subpressor rate of ANG II ($500 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) to apoE^{-/-} mice results in an increased aortic lumen diameter. Aortic diameters of ANG II-infused mice were increased compared with measurements before infusion. Data are means \pm SE from $n = 5$ mice/group. *Significantly different from saline (day 28) and from baseline value, $P < 0.05$.

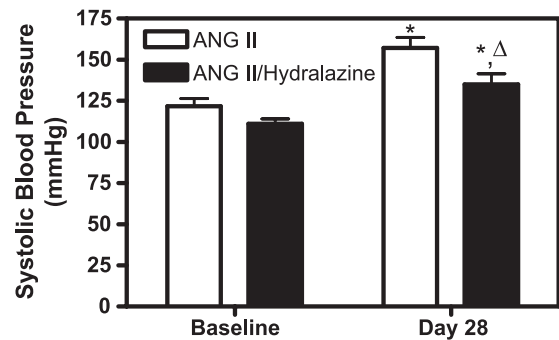


Fig. 4. Administration of hydralazine reduces ANG II-induced increases in systolic blood pressure. Infusion of ANG II increased systolic blood pressure in mice administered either vehicle or hydralazine. However, systolic blood pressures were lower in ANG II-infused mice administered hydralazine compared with vehicle. Data are means \pm SE from $n = 10$ mice/group. *Significantly different from baseline; Δ significantly different from ANG II, $P < 0.05$.

Infusion of two vasoconstrictive drugs that caused equivalent blood pressure increases in two different hypercholesterolemic mouse models resulted in greatly disparate AAA formation. Moreover, infusion of ANG II at a rate that did not significantly elevate blood pressure resulted in a 50% AAA incidence. Finally, attenuation of ANG II-induced increases in blood pressure by a concomitant administration of a vasodilator did not influence development of AAAs. Thus elevations in blood pressure from infusion of ANG II do not significantly contribute to AAA pathology.

Previous studies have demonstrated that ANG II-induced increases in blood pressure were not the direct cause of the profound increases in atherosclerotic lesion size that occur during chronic subcutaneous infusion of ANG II (33). The present study confirmed this response, and extended these findings to ANG II-induced AAAs. Similar findings across these two disparate vascular pathologies induced by infusion of ANG II are surprising, since these pathologies have a very different evolution (31). Unlike atherosclerosis in which changes are restricted to the intima, AAAs involve changes in the media. The formative stage of ANG II-induced AAAs exhibits degradation of medial extracellular matrix and subsequent medial rupture, with subsequent complex cellular changes in the intimal, media, and adventitia of evolving AAAs (31). Moreover, the cellular targets of ANG II may differ across these vascular pathologies, since deficiency of angiotensin type 1a receptors on bone marrow-derived cells modestly decreased ANG II-induced atherosclerosis but had no effect on AAA formation (6). Despite differences in cell targets and mediators of ANG II to promote atherosclerosis and AAA formation, results from this study demonstrate that elevated

blood pressure is not a primary contributor to either of these pathologies.

Indirect evidence has been supplied in other studies that are consistent with the notion that increased blood pressure per se does not directly affect ANG II-induced AAA formation. Several other studies have inferred dissociation of blood pressure and ANG II-induced AAAs. Administration of doxycycline, an inhibitor of matrix metalloproteinases, to LDLr^{-/-} mice reduced ANG II-induced AAAs, but had no effect on blood pressure (26). Similarly, administration of vitamin E (16), β -estradiol (27), or a cyclooxygenase 2 inhibitor (22) to hypercholesterolemic mice reduced ANG II-induced AAA formation, without abrogating elevations in blood pressure. Genetic deficiencies of BLT1^{-/-} (1), osteopontin (4), or urokinase plasminogen activator (14) in hypercholesterolemic mice all reduced ANG II-induced AAAs, but again did not alter the hypertensive response to ANG II. Moreover, castration of male apoE^{-/-} mice ablated ANG II-induced AAAs (19), whereas administration of exogenous dihydrotestosterone to castrated male and female apoE^{-/-} mice increased AAAs (18), with no discernable influences on blood pressure. Conversely, administration of PD-123319, an angiotensin type 2 receptor antagonist, increased ANG II-induced AAAs in apoE^{-/-} mice, with no effects on blood pressure (9). These results demonstrate that ANG II-induced AAAs are markedly regulated by manipulations that do not influence blood pressure, providing indirect evidence for independence of AAA formation from blood pressure.

The magnitude of blood pressure elevations (~ 25 mmHg) from this infusion rate of ANG II, as measured by radiotelemetry, are in agreement with previous studies in mice using tail cuff methods (6, 19). However, ANG II-induced elevations in blood pressure in apoE^{-/-} or LDLr^{-/-} mice were far less than observed in rats infused at similar rates with ANG II (5). In previous studies, we examined mechanisms contributing to differences between rats and mice in their responses to infused ANG II (5). Plasma concentrations of angiotensin peptides were greater in mice compared with rats, and we were unable to detect a further increase in plasma angiotensin concentrations in mice upon infusion of ANG II. Other species differences in the renin-angiotensin system may contribute to the modest increase in blood pressure in mice in response to high

Table 2. Characteristics of ANG II-infused apoE^{-/-} mice administered with either vehicle or hydralazine

	Infusions	
	Vehicle	Hydralazine
Body wt, g	27.6 \pm 0.5	28.2 \pm 0.9
Serum cholesterol concentrations, mg/dl	289 \pm 25	313 \pm 26
Plasma renin concentrations, ng/ml	1.07 \pm 0.37	0.61 \pm 0.07

Data are means \pm SE from $n = 10$ mice/group. All comparisons were not significant.

infusion rates of ANG II (5). Regardless, results from this study demonstrate that the modest hypertension during ANG II infusion in hypercholesterolemic mice is not a major contributor to the marked vascular pathologies elicited by infusion of this peptide.

Relatively few studies have examined the effects of hypertension in other animal models of AAAs. In hypertensive angiotensinogen and renin transgenic mice that overproduce ANG II, excessive salt intake increased aortic aneurysms and rupture (28). However, aneurysms did not occur unless transgenic mice were fed a high-salt diet, even though blood pressure was not increased further by salt intake. In genetically hypertensive rats with aneurysms induced by perfusion of elastase, propranolol reduced AAA size but had no effect on blood pressure (32). Thus other models of experimental AAAs appear to be independent of blood pressure; however, contrasting results have been reported (15, 30).

The ANG II infusion model of AAA formation has similarities and differences to human AAAs (9). Because AAAs form readily during ANG II infusion in hypercholesterolemic mice, this model recreates the clinical situation where hypercholesterolemia, atherosclerosis, and hypertension are frequently present in AAA patients. Results from population studies suggest that hypertension is a relatively weak risk factor for AAAs (23). As a therapeutic treatment, the β -receptor antagonist propranolol lowered blood pressure but did not affect expansion of aneurysms, need for surgical repair, or mortality in patients with aortic aneurysms (21, 24). In contrast, in a population-based case-control study, angiotensin-converting enzyme inhibitors, but not other antihypertensive agents, reduced risk of ruptured AAAs (17). An angiotensin type 1 (AT₁) receptor antagonist was one of the other antihypertensive agents that did not reduce rupture of AAAs; however, the sample size in this treatment group was insufficient to draw meaningful conclusions. Thus it is unclear whether AT₁ receptor antagonism would confer the same reduced risk of AAA rupture. Interestingly, in a small cohort study of patients with Marfan's syndrome, losartan was effective at slowing the rate of progressive aortic-root dilation (3) and is now under study within a randomized trial. Although results from this study do not support a predominant role of hypertension in ANG II-induced AAAs, they do support the potential utility of inhibitors of the renin-angiotensin system in the medical treatment of AAAs.

In conclusion, the present findings demonstrate that ANG II-induced AAAs develop by mechanisms that are independent of blood pressure and confirm that augmentation of atherosclerosis by infusion of ANG II occurs independently of ANG II-induced hypertension. It is intriguing that infusion of ANG II is capable of inducing two distinct vascular pathologies with effects unrelated to elevations in blood pressure. These results suggest that other effects of ANG II, presumably related to mechanisms of inflammation in these diverse vascular pathologies, primarily mediate the effects of ANG II. Moreover, these results suggest that drugs directed at inhibition of the renin-angiotensin system may exert beneficial therapeutic effects on atherosclerosis and/or AAA at doses that do not lower blood pressure. Future studies should address the clinical efficacy of inhibition of the renin-angiotensin system against AAA development and progression.

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