Angiotensin II Infusion Promotes Abdominal Aortic Aneurysms Independent of Increased Blood Pressure in Hypercholesterolemic Mice

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Running head: Blood pressure independence of angiotensin II-induced AAAs

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Abstract

Infusion of angiotensin II (AngII) into hyperlipidemic mice augments atherosclerosis and causes formation of abdominal aortic aneurysms (AAAs). The purpose of this study was to define the contribution of AngII-induced hypertension to these vascular pathologies. Male apolipoprotein E (apoE) and LDL receptor (LDLr) deficient mice were infused with AngII (1,000 ng/kg/min) or norepinephrine (NE; 5.6 mg/kg/day) for 28 days. Infusion of AngII or NE increased mean arterial pressure (MAP; AngII, 133 ± 2.8; NE, 129 ± 13 mmHg) to a similar extent compared to baseline blood pressures (MAP, 107 ± 2 mmHg). Abdominal aortic width increased in both apoE-/- or LDLr-/- mice infused with AngII (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 AngII compared to NE. At a subpressor infusion rate of AngII (500 ng/kg/min), AAAs developed in 50% of apoE-/- mice. Alternatively, administration of hydralazine (250 mg/L) to AngII-infused apoE-/- mice (1,000 ng/kg/min) lowered systolic blood pressure (day 28: AngII, 157 ± 6; AngII/hydralazine, 135 ± 6 mmHg), but did not prevent AAA formation or atherosclerosis. These results demonstrate that infusion of AngII to hyperlipidemic mice induces AAAs and augments atherosclerosis independent of increased blood pressure.

Keywords: Aneurysms, hypertension, vascular lesions
Introduction

Angiotensin II (AngII) 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 (RAS) contributes to the development of other vascular diseases, including atherosclerosis and abdominal aortic aneurysms (AAAs) (9,25). Several lines of evidence have demonstrated that AngII does not promote atherosclerosis through an indirect effect of increased blood pressure (25). This evidence includes the contrasting effects of chronic infusion of AngII 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 2-kidney, 1-clip surgery compared to non-renin dependent hypertension induced by 1-kidney, 1-clip surgery (20).

In contrast to the well-characterized independence of blood pressure on AngII-induced atherosclerosis (33), the contribution of pressure *per se* to the development of AngII-induced AAAs has not been defined. This is important since AngII-induced atherosclerosis and AAAs are distinct vascular pathologies with disparate mechanisms (31). AAAs formed from infusion of AngII are characterized by a large luminal expansion due to disrupted medial elastin within the first 10 days of AngII-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 AngII
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 AngII 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 are complicated by the definition of hypertension (based on treatment for the condition). Also, antihypertensive drugs may influence the development of AAA independent of their blood pressure lowering effects. At infusion doses typically employed to induce AAAs in hyperlipidemic mice, the AngII 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 AngII-induced increases in blood pressure to AAA formation. This was accomplished by contrasting the effects of infusions of either AngII or NE at rates that elevated blood pressure to a similar extent in the two most commonly used strains of mice for AAA studies; apoE-/- and LDLr-/- mice (7,10). As a second approach, we defined effects of sub-pressor infusion rates of AngII to apoE-/- mice on AAA formation. Finally, we determined the effects of attenuating AngII-induced blood pressure increases by the concomitant infusion of hydralazine. These studies demonstrated that blood pressure per se is not a major determinant of AngII-induced AAAs.
Methods

Animals and drug infusions. Male LDLr-/- and apoE-/- (2 months of age; backcrossed 10 times onto a C57BL/6 background) were originally obtained from the Jackson Laboratory (Bar Harbor, ME) and maintained at the University 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 week prior, and 4 weeks during, AngII infusion. Both apoE-/- and LDLr-/- were infused with either AngII (1,000 ng/kg/min; n = 26) or NE (5.6 mg/kg/day; n = 26) by osmotic minipump (Model 2004, Durect Corp) for 28 days. Other studies examined effects of sub-pressor infusion rates of AngII (500 ng/kg/min; 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 week prior to, and throughout, infusion of AngII (1,000 ng/kg/min for 28 days; n = 12/group, control versus 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 months of age) were infused with either AngII (1,000 ng/kg/min) or NE (5.6 mg/kg/day; n = 6/group). Mice were anesthetized with isoflurane and left carotid arteries were isolated. Telemeter catheters were inserted into 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 week before obtaining baseline measurements of blood pressure (3 consecutive days at 24 hours/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 Dataquest ART 2.3 acquisition system (Data Sciences International). The system was programmed to acquire data for 10 seconds every minute, and to calculate 10 minute 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 5 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). Since 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, i.p. 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, i.p.) by left ventricular puncture into tubes containing EDTA (0.05M). Plasma was obtained by centrifugation (5,000 rpm) at 4°C for 10 minutes. Plasma renin concentrations were measured by incubating (37°C, 30 minutes) 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 angiotensin I, followed by radioimmunoassay (6,12). Total serum cholesterol concentrations were measured as described previously (25).

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

Infusions of AngII and NE promote similar increases in blood pressure but have disparate effects on AAAs and atherosclerosis

Infusions of either AngII 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). Since 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 to apoE-/- mice. In agreement with previous results demonstrating that infusion of AngII results in negative feedback inhibition of kidney-derived renin (6,18), plasma renin concentrations were lower in mice infused with AngII compared to NE. In apoE-/- mice infused with AngII or NE, systolic, diastolic and mean arterial pressure increased within one day of infusion and were elevated for 16 days (Figure 1A, online Table I). In addition, mice infused with AngII exhibited similar blood pressure elevations to those infused with NE. Heart rate and pulse pressures were not different in apoE-/- mice infused with AngII or NE (online Table I). In LDLr-/- mice infused with either AngII 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 AngII infusion into apoE-/- and LDLr-/- mice resulted in increased lumen diameters of suprarenal abdominal aortas compared to measurements prior to infusion (Figure 1B). In contrast, NE infusion into apoE-/- and LDLr-/- mice did not increase lumen diameter (Figure 1B), or promote aneurysmal pathology.
AAA incidence was similar in apoE-/- and LDLr-/- infused with AngII (53 and 47%, respectively), but no AAAs formed in mice infused with NE (Supplemental Figure I). Measurements of excised aortas demonstrated that maximal width of suprarenal abdominal aortas were increased in both apoE-/- and LDLr-/- mice infused with AngII, but not in mice infused with NE (Figure 1C). In agreement with many studies, infusion of AngII increased the aortic intima areas of atherosclerosis. In accord with the findings of Weiss et al (33), NE infusions into these mice promotes a much lesser increase in atherosclerosis area (Figure 2).

**Infusion of sub-pressor doses of AngII promote AAA formation**

Infusion of AngII at 500 ng/kg/min to apoE-/- mice did not influence body weight (saline, 26.3 ± 1.3; AngII, 24.9 ± 1.3 g). Systolic blood pressure was not significantly different in mice infused with saline compared to AngII (saline, 117 ± 2; AngII, 130 ± 6 mmHg, p = 0.08). Aortic lumen diameters were increased compared to measurements prior to infusion in mice infused with AngII, but not saline (Figure 3), resulting in a 50% AAA incidence.

**Attenuation of AngII-induced increases in blood pressure did not influence development of atherosclerosis or AAA formation**

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

Abdominal aortic lumen diameters on day 28 of AngII infusion were not significantly different in apoE-/- mice administered hydralazine compared to vehicle (1.59 ± 0.21 versus 1.38 ± 0.03, respectively). AAA incidence was also not significantly different in AngII-infused mice administered hydralazine or vehicle (58 versus 50%, respectively). Finally, atherosclerotic lesions areas were not significantly influenced by administration of hydralazine to AngII-infused mice (hydralazine: 3.00 ± 0.40; vehicle: 1.74 ± 0.50 mm²; p = 0.06).
Discussion

This study demonstrated that AAA formation resulting from infusion of AngII to hypercholesterolemic mice occurs independent of blood pressure elevating effects of the octapeptide. 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 AngII at a rate that did not significantly elevate blood pressure resulted in a 50% AAA incidence. Finally, attenuation of AngII-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 AngII do not significantly contribute to AAA pathology.

Previous studies have demonstrated that AngII-induced increases in blood pressure were not the direct cause of the profound increases in atherosclerosis lesion size that occur during chronic subcutaneous infusion of AngII (33). The present study confirmed this response, and extended these findings to AngII-induced AAAs. Similar findings across these two disparate vascular pathologies induced by infusion of AngII 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 AngII-induced AAAs exhibits degradation of medial extracellular matrix and subsequent medial rupture, with subsequent complex cellular changes in the intimal, media, and adventitia of the evolving AAA (31). Moreover, the cellular targets of AngII may differ across these vascular pathologies, since deficiency of angiotensin type 1a receptors (AT1aR) on bone marrow derived cells modestly
decreased AngII-induced atherosclerosis, but had no effect on AAA formation (6). Despite differences in cell targets and mediators of AngII 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 AngII-induced AAA formation. Several other studies have inferred dissociation of blood pressure and AngII-induced AAAs. Administration of doxycycline, an inhibitor of MMPs, to LDLr-/- mice reduced AngII-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 AngII-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 AngII-induced AAAs, but again did not alter the hypertensive response to AngII. Moreover, castration of male apoE-/- mice ablated AngII-induced AAAs (19), while administration of exogenous dihydrotestosterone to castrated male and female apoE-/- mice increased AAAs (18), with no discernable influences on blood pressure. Conversely, administration of PD123319, an AT2 receptor antagonist, increased AngII-induced AAAs in apoE-/- mice, with no effects on blood pressure (9). These results demonstrate that AngII-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 (approximately 25 mmHg) from this infusion rate of AngII, as measured by radiotelemetry, are in agreement with previous studies in mice using tail cuff methods (6,19). However, AngII-induced elevations in blood pressure in apoE-/- or LDLr-/- mice were far less than observed in rats infused at similar rates with AngII (5). In previous studies, we examined mechanisms contributing to differences between rats and mice in their responses to infused AngII (5). Plasma concentrations of angiotensin peptides were greater in mice compared to rats, and we were unable to detect a further increase in plasma angiotensin concentrations in mice upon infusion of AngII. Other species differences in the renin-angiotensin system may contribute to the modest increase in blood pressure in mice in response to high infusion rates of AngII (5). Regardless, results from this study demonstrate that the modest hypertension during AngII infusion into 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 AngII, 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 further increased 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 AngII infusion model of AAA formation has similarities and differences to human AAAs (9). Since AAAs form readily during AngII infusion into 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 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, ACE inhibitors, but not other antihypertensive agents, reduced risk of ruptured AAAs (17). An 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. While results from this study do not support a predominant role of hypertension in AngII-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 AngII-induced AAAs develop by mechanisms that are independent of blood pressure, and confirm that augmentation of atherosclerosis by infusion of AngII occurs independently of AngII-induced
hypertension. It is intriguing that infusion of AngII is capable of inducing two distinct vascular pathologies with effects unrelated to elevations in blood pressure. These results suggest that other effects of AngII, presumably related to mechanisms of inflammation in these diverse vascular pathologies, primarily mediate the effects of AngII. 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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Disclosures

There are no conflicts of interest.
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Figure Legends

Figure 1. Infusions of either AngII or NE increase MAP, but only AngII promotes AAA formation. A, MAP was increased to a similar extent by infusions of either AngII or NE. B, Aortic lumen diameters were increased by infusions of AngII in apoE-/- or LDLr-/- mice compared to measurements prior to infusion. In contrast, infusions of NE did not change baseline aortic lumen diameters. C, External diameter (maximal width) of suprarenal abdominal aortas from apoE-/- or LDLr-/- mice infused with either saline or AngII. Data are mean ± SEM from n = 6 mice/group (A), or n = 26 mice/group/treatment (B,C). *, Denotes significantly different from baseline (A), from baseline (0) and NE (B), or from NE (C).

Figure 2. Atherosclerotic lesions were increased to a greater extent by infusion of AngII (n = 26/genotype) compared to NE (n = 26/genotype) in both apoE-/- and LDLr-/- mice. Lesion areas were greater in LDLr-/- compared to apoE-/- mice, regardless of drug infusions. Lesion areas were greater in mice infused with AngII compared to NE, regardless of genotype. Symbols represent individual mice, with mean ± SEM to the right of each group. *, Denotes significantly different from NE, P< 0.05.

Figure 3. Infusion of a subpressor rate of AngII (500 ng/kg/min) to apoE-/- mice results in an increased aortic lumen diameter. Aortic diameters of AngII-infused mice were increased compared to measurements prior to infusion. Data are mean ± SEM from n = 5 mice/group. *, Denotes significantly different from saline (day 28) and from baseline value, P < 0.05.
Figure 4. Administration of hydralazine reduces AngII-induced increases in systolic blood pressure. Infusion of AngII increased systolic blood pressure in mice administered either vehicle or hydralazine. However, systolic blood pressures were lower in AngII-infused mice administered hydralazine compared to vehicle. Data are mean ± SEM from $n = 10$ mice/group. *, significantly different from baseline; ∆, significantly different from AngII, $P < 0.05$. 
<table>
<thead>
<tr>
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<th>NE (LDLr-/-)</th>
<th>NE (ApoE-/-)</th>
<th>AngII (LDLr-/-)</th>
<th>AngII (ApoE-/-)</th>
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<td>Body weight (g)</td>
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<td>28.1 ± 0.3</td>
<td>28.1 ± 0.5</td>
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<td>concentration (mg/dL)</td>
<td>1,262 ± 102</td>
<td>368 ± 25*</td>
<td>1,403 ± 74</td>
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<td>concentration (ng/ml)</td>
<td>5.79 ± 0.78</td>
<td>3.56 ± 0.61*</td>
<td>1.55 ± 0.30**</td>
<td>0.86 ± 0.07*,**</td>
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</table>

Data are mean ± SEM from n = 26 mice/group.

*, significantly different from LDLr-/- within infusions, P < 0.05.

**, significantly different from NE within strains, P < 0.05.
Table 2. Characteristics of AngII-infused apoE-/- mice administered with either vehicle or hydralazine.

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Hydralazine</th>
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<td>Body weight (g)</td>
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<td>28.2 ± 0.9</td>
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<td>Serum cholesterol concentrations (mg/dL)</td>
<td>289 ± 25</td>
<td>313 ± 26</td>
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<td>Plasma renin concentrations (ng/ml)</td>
<td>1.07 ± 0.37</td>
<td>0.61 ± 0.07</td>
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</table>

Data are mean ± SEM from n = 10 mice/group.

All comparisons were not significant.
Fig. 1
Fig. 2
Fig. 3

Aortic Lumen Diameter (mm)

Baseline | Day 28
--- | ---
Saline | AngII

*Significant difference