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The Role of the Renin-Angiotensin System in Aortic Aneurysmal Diseases

Hong Lu[1], **Debra L. Rateri**[1], **Lisa A. Cassis**[1,2], and **Alan Daugherty**[1,2]

[1]Cardiovascular Research Center, University of Kentucky, Lexington, Kentucky

[2]Graduate Center for Nutritional Sciences, University of Kentucky, Lexington, Kentucky

Abstract

The renin angiotensin system (RAS) has been invoked in the development of both abdominal and thoracic aortic aneurysms. Experimentally, this has been demonstrated by the chronic subcutaneous infusion of angiotensin II (AngII) that consistently leads to the development of abdominal aortic aneurysms (AAAs) in mice. AngII-induced AAAs have highly heterogenous cellular and extracellular matrix characteristics throughout the aorta that change markedly with duration of infusion. The mechanistic basis for the reproducible location of AAA development has not been elucidated, but many recent insights have been provided especially in regard to receptor and inflammatory mechanisms. A recent clinical study has provided some limited evidence for the extrapolation of these results to mechanisms of human AAAs. Experimental evidence has also demonstrated that antagonism of AT1 receptors prevents ascending aortic aneurysms in a mouse model of Marfan's disease. A clinical study is currently ongoing to demonstrate the efficacy of antagonism of AT1 receptors in humans.

Introduction

An aneurysm is defined as a permanent dilation, although there are complexities related to age, gender, and reference points regarding the acceptance of criteria for considering an aneurysm as being pathological [1]. Aneurysms may occur in several blood vessels, with aortic aneurysms occurring in both the thoracic and abdominal regions. Aneurysms frequently develop in a covert manner, but have dramatic clinical presentations caused by rupture with high mortality. AAAs account for large numbers of deaths, although the incidence of AAA-related death is probably vastly underestimated given our inability to discriminate it from other forms of cardiovascular related deaths in the absence of an autopsy. Although aneurysms of the ascending aortic arch are much lower in incidence, they are the major cause of mortality in individuals afflicted with Marfan's and similar diseases [2].

Unfortunately, there is limited mechanistic insight into the initiation and propagation of aneurysms. The current treatment option is surgical repair with its attendant complications and risks. This surgical option only treats the end stage of the disease when the threat of rupture is considered to be imminent. For both abdominal and thoracic aortic aneurysms, there are no medically proven modes of treatment. The inability to implement an effective pharmacological therapy during the formative or progressive stages of the disease is partially due to our lack of knowledge of mechanisms responsible for aortic dilation. However, there is a consistent and evolving literature that inappropriate activity of the RAS is an underlying cause of aortic

Address for Correspondence: Alan Daugherty, Cardiovascular Research Center, Wethington Building, Room 521, University of Kentucky, Lexington, KY 40536-0200, Telephone: (859) 323-4933 x 81389, Fax: (859) 257-3646, Alan.Daugherty@uky.edu.

aneurysmal diseases. We previously reviewed this evidence in 2004, and therefore will primarily focus on publications since that time [3].

AngII Infusion Induces Complex and Progressive AAAs

A number of different animal species have generated experimental models of AAAs. However, mice are the most commonly used species in contemporary studies [4]. The most frequently used mouse models of AAAs are: 1. Intra-lumenal infusion of porcine elastase into the infra-renal aorta; 2. Peri-aortic incubation of a high concentration solution of calcium chloride; 3. Subcutaneous infusion of AngII into normo-or hypercholesterolemic mice [4]. These 3 mouse models all yield pronounced changes that are most overt in the medial and adventitial aspects of the aorta.

Chronic subcutaneous AngII infusion into male apoE -/- or LDL receptor -/- mice has consistently led to generation of pronounced AAAs that are located in the suprarenal aorta [5-16]. AngII infusion also induces AAAs of similar gross appearance in normolipidemic mice, although with a lesser incidence [17]. The development of AngII-induced AAAs shows a strong gender preference, with much greater incidence in males, as occurs in the human disease [18, 19].

AAAs induced by AngII-infusion have complex cellular and extracellular matrix characteristics that can vary greatly along the length of the aorta. In addition, continued AngII infusion leads to progressive changes in the pathological characteristics of the aneurysmal tissue. The earliest cellular change noted following initiation of AngII infusion is medial accumulation of macrophages in the AAA-prone area. This occurs in regions of limited elastin breaks and precedes disruption of elastin fibers across the entire medial layer [20]. Medial disruption does not usually lead to a loss of vessel patency, but contributes to large expansions of luminal diameter and thrombus formation. The recent development of very high frequency ultrasound has enabled a time course of luminal expansion of abdominal aortas to be measured noninvasively during AngII infusion [21]. AngII infusion promotes and initial rapid phase of lumen expansion within the first 5 days. This is followed by a more gradual increase in luminal diameter. This large luminal expansion is also present in histological sections [6,20]. However, it is usually bordered, both proximally and distally, by regions of adventitial thickening. This initial phase of luminal dilation is followed by modest further expansion that is associated with pronounced remodeling of the aorta. During this phase there is accumulation of macrophages, T and B lymphocytes. The lumen in the AAA regions becomes re-endothelialized, and there is frequent formation of a “neomedia”. Atherosclerotic lesions develop in these established AAAs.

Recent studies have examined the progression of AAAs during infusions of AngII up to 3 months. Continuous AngII infusion leads to progressive luminal expansion as measured by sequential noninvasive monitoring with high frequency ultrasound. Luminal expansion is variable among individual mice, but may enlarge to over 4 mm in mice that have baseline diameters of approximately 0.8 mm. Occasionally, mice die from AAA rupture during these prolonged infusions [22]. Cessation of AngII infusion after 1 month of infusion in mice with ultrasonically-verified increased luminal diameters does not lead to further dilation during the subsequent 2 months. Similarly, the incidence of AAA rupture is minimal. However, termination of AngII infusion also does not lead to any observable reduction in the size and severity of AAAs [22]. Although one study has noted a complete regression of AngII-induced AAAs following discontinuation of infusion, this study was performed in female mice that have a low incidence of AAAs. In addition, the presence of AAAs was not verified noninvasively as being dilated [11].

Overall, the infusion of AngII has led to the appearance of AAAs located to the suprarenal aorta, as replicated by multiple laboratories using this model. The heterogeneity and progressive changes have led to some confusion regarding the pathological characteristics of AngII-induced AAAs. However, it is clear that AngII-induced AAAs in mice have many similar characteristics to the human disease including profound increases in luminal diameter, medial degeneration, extracellular matrix disruption, leukocyte infiltration, thrombus formation, and atherosclerotic lesions [23·].

Roles of the RAS in Experimental AAAs

The role of the RAS in formation of AAAs is partially based on associations of the components of the system being present in experimental aneurysmal tissue. Traditionally, the RAS has been considered as a systemic pathway for synthesized peptides that exert local effects depending on the presence of angiotensin receptors. These effects are through predominantly AT1 receptors, with a less defined role for the function of AT2 receptors. However, it is becoming apparent that angiotensin peptides are synthesized locally, either through the classic pathway involving renin and ACE, or alternative pathways.

A limited number of studies have detected components of the classic RAS in experimental aneurysmal tissue. This has included the detection of both mRNA and protein for ACE in elastase-induced aneurysmal tissue of rats. No changes were noted in mRNA abundance for AT1 or AT2 receptors [12]. Evidence for a role of ACE in experimental AAAs was provided by three inhibitors of the enzyme (captopril, lisinopril, and enalapril) that reduced the aortic diameter and decreased elastin degradation in elastase-perfused rats [24]. However, the lack of effect of the AT1 receptor antagonist, losartan, does confound the interpretation of a role of AngII in elastase-induced aneurysms.

Chymase has been invoked as a potential alternative enzyme to ACE for the generation of AngII from AngI. In dogs, chymase has been detected in elastase-induced aneurysmal tissues and associated with increased ability to form AngII. The active role of chymase was proven by administration of an inhibitor, NK3201, that attenuated the ultrasonically-defined luminal expansion and maintained the medial layer [25]. A major cell type for secretion of chymase is mast cells. Recently, mast cell deficiency has been shown to attenuate elastase and calcium chloride induced AAAs in mice, although these studies did not evoke a role of chymase.

Early studies in the AngII-induced AAA model demonstrated that the AT1 antagonist, losartan, ablated development of the pathology [26]. Mice express 2 subtypes of AT1 receptors that are highly homologous, but display functional differences. For example, the AT1b receptor subtype is abundantly expressed in aorta and is responsible for AngII-induced contractions of the abdominal aorta. Despite the abundance of AT1b receptors in aortas, deficiency of the AT1a receptor subtype completely ablated the development of AngII induced AAAs [27]. Bone marrow transplantation studies were subsequently performed to determine whether AngII-induced AAAs were due to stimulation of AT1a receptors on donor bone marrow derived or recipient cells. These studies had the confounding issue that the irradiation and repopulation procedure influenced the development of AngII-induced AAAs [27]. Nevertheless, these studies clearly demonstrated that the AT1a receptor genotype of the recipient had a major effect on development of AngII-induced AAAs (Table 1). In contrast, deficiency of AT1a receptors on repopulated bone marrow derived cells had no effect on AngII-induced AAAs [27]. It has not been determined which recipient cell types express AT1a receptors to regulate the disease, but likely candidates are endothelial and smooth muscle cells. We are currently addressing this issue using LDL receptor -/- mice that have floxed AT1a receptors.

One potential consequence of RAS activation from AngII infusion is increased plasma concentrations of aldosterone, which has been attributed as the mediator of AngII-mediated

vascular inflammation. However, infusion of multiple doses of aldosterone, that resulted in progressive increases in circulating aldosterone concentrations, into male apoE-/- mice failed to generate AAAs that are a characteristic of AngII infusion [28]. In addition, the aldosterone receptor antagonist, spironolactone, failed to influence AngII-induced AAAs. Therefore, although aldosterone regulates some AngII-induced inflammatory effects, it is not involved in the development of AAAs.

Mechanistic Studies on AngII-induced AAAs

We focus in this section on AngII-induced AAAs as a relatively simple model invoked by infusion of AngII through subcutaneous implantation of mini-osmotic pumps, with an easily defined end-point of dilations of abdominal aortas. Thus, a relatively large number of publications have investigated various facets of AngII-induced AAAs (Table 1).

A feature of all stages of AngII-induced AAAs is the accumulation of macrophages. Monocyte chemoattractant protein-1 is one of the most prominent chemokines that has been invoked in macrophage-based vascular pathologies through interaction with its receptor, CCR2. Whole body deficiency of CCR2 attenuated the development of AngII-induced AAAs [29]. Although CCR2 may present on multiple cell types, its expression on bone marrow derived cells is critical for the development of AngII-induced AAAs [8,29].

The complex prostanoid family has been implicated in many inflammatory processes. Bioactive lipids of this family are derived from PGH2 that is the product of both cyclooxgenase (COX) enzymes, COX-1 and COX-2. Both COX enzymes catalyze the same reaction. However, they impart different biological responses based on the differential location of their expression, and that of downstream processing enzymes and receptors for the specific bioactive lipid products. COX-2 mRNA abundance increased in mouse abdominal aortas during progressive lengths of AngII infusion. This was not associated with increased abundance of mPGES-1 which may infer that PGE2 synthesis was not increased [30]. Inhibition of COX-2 in male apoE-/- mice using the relatively selective inhibitor, celecoxib, led to reduced AAA incidence and severity [31]. The role of COX-2 was also studied in genetically deficient mice with a hybrid genetic background of C57BL/6 and 129/Ola. This genetic background showed increased susceptibility to AngII-induced AAAs compared to normolipidemic C57BL/6 mice [17], that was attenuated with COX-2 deficiency [30]. In contrast, pharmacological inhibition of COX-1 with SC-560 failed to alter characteristics of AngII-induced AAAs in male apoE -/- mice [31].

Lipoxygenases also form a range of bioactive lipids derived from arachidonic acid. A role for 5-lipoxygenase has been inferred through the attenuation of hyperlipidemic induced aortic aneurysms in apoE -/- mice by deficiency of this enzyme [14]. The leukotriene B(4) formed by 5-lipoxygenase exerts its biological effects through interaction with the G protein coupled receptor, BLT-1. Consistent with a role in the disease, deficiency of BLT-1 reduces AngII-induced AAAs in apoE-/- mice [15]. However, in a recent publication, deficiency and pharmacological inhibition of 5-lipoxygenase failed to influence the development of AngII-induced AAAs in apoE-/- mice [14]. Thus, there is a need for further studies to clarify the role of these pathways.

In addition to phospholipid-based inflammatory responses, interferon beta (IFN-β) has been investigated due to its inhibitory effects on inflammatory responses. Subcutaneous injection of IFN-β attenuated AngII-induced atherosclerosis, but had no effect on AngII-induced AAA formation in apoE -/- mice [32]. This is one of several studies in a range of animal models of AAAs that have dissociated effects on aneurysm formation versus atherosclerosis [33].

AngII-induced AAAs are associated with the presence of matrix metalloproteinases (MMPs). Since extracellular matrix destruction is a hallmark of AAAs, the ability of these enzymes to fragment elastin and collagen make them candidates for mediators of the disease. There have been particular emphases on MMP-2 and MMP-9 that degrade both elastin and denatured collagens. Both MMP-2 and MMP-9 have been detected by zymography in extracts of AngII-induced AAAs [7,12]. MT1-MMP was also detected in these tissues [12].

The syndecans are a family of cell surface proteoglycans that can bind and modulate the activity of a diverse group of ligands, including MMP-1, 2, and 9. Infusion of AngII into apoE-/- mice for 1, 4 or 8 weeks while concurrently consuming a fat-enriched diet increased syndecan-1 expression in infiltrating macrophages that predominantly localized to the adventitia. Macrophage-associated syndecan-1 expression was accentuated during the course of aneurysm formation [34]. During development of aneurysms, syndecan-2 was abundantly expressed within aortic thrombi, and syndecan-4 was observed within aortic medias. Taken together, subtypes of syndecans may play different roles in the genesis and development of AngII-induced AAAs through regulation of the local inflammatory and proteolytic environment in the vascular wall.

To date, there have been no publications on the effects of genetic deficiencies of any MMPs on the development of AngII-induced AAAs. An implication of the role of MMPs is derived from pharmacological inhibitors. Although doxycycline is well known as an antimicrobial drug, it has been used in AAA studies to inhibit a broad spectrum of MMPs. In agreement with a role for MMPs, doxycycline attenuates AAAs when administered to LDL receptor -/- mice prior to initiation of AngII infusion [33]. Another pharmacological approach for reducing MMP activity has been to inhibit histone deacetylase. The inhibitor, metacept, reduced AngII-induced AAAs in male apoE -/- mice [16]. Both studies used inhibitors that are non selective for specific MMPs and have the potential for effects on non MMP targets. Thus, there is a need for further studies with either specific genetic deficiencies or more selective pharmacological tools.

Reactive oxygen species (ROS) have the potential to influence AAA development by regulation of inflammation, MMP activation, and smooth muscle cell apoptosis. Many compounds have antioxidant properties, including vitamins E and C. An initial study demonstrated that dietary enrichment with vitamin E attenuated the formation of AngII-induced AAAs in apoE-/- mice [9]. A subsequent study used dietary supplementation of both vitamin E and C, but failed to demonstrate an effect on AngII-induced AAAs in apoE -/- mice, as defined by aortic rupture [35]. The authors suggested the age of the mice (50 - 60 weeks of age at the start of the study) as a potential explanation for the lack of effect of combined vitamin E and C supplementation.

A major source of ROS in vascular tissue is membrane-bound NADPH oxidase, which consists of transmembrane (eg, NOX1, NOX2, NOX4, and p22phox) and cytosolic (p47phox, p67phox, and rac) subunits that assemble to form the functional oxidase. Deficiency of p47phox attenuates AngII-induced AAAs in male apoE -/- mice [36]. NOX1 deficiency decreased AngII-induced AAAs in mice that were backcrossed six times into a C57BL/6 background [37]. This study demonstrated that norepinephrine-induced increases in blood pressure, equivalent to that generated by AngII infusion, failed to develop AAAs. Therefore, there is limited, but consistent data for a role of the NADPH oxidase system on development of AngII-induced AAAs.

Pharmacological targeting of intracellular signaling has further provided mechanistic insights in AngII-induced AAAs in animal models. Fasudil, a Rho-kinase inhibitor, attenuated AngII-induced AAAs in apoE-/- mice by inhibiting apoptosis and proteolysis [38]. More recently, it has been demonstrated that the JNK inhibitor, SP600125, attenuated the development of

calcium chloride induced AAAs [13··]. This was associated with changes in molecules that are critical to extracellular matrix biosynthesis, such as lysyl oxidase. More surprisingly, it was demonstrated that the JNK inhibitor regressed established AAAs when they were generated by either calcium chloride or AngII-infusion. As part of their efforts to study regression, AngII was infused into male apoE-/- mice for 4 weeks and the diameter of the aorta was measured using a clinical ultrasound machine that operated at 15 MHz. In the subsequent 8 weeks, there was an 18% reduction in luminal diameter in mice administered with SP600125, while there was no change in mice administered with vehicle. These provocative results are the first demonstration that AAAs may regress. These results need confirmation and further probing into the mechanistic basis for this regression.

The incidence of AngII-induced AAAs is much greater in male than female mice, as is the case in humans [18,19]. This difference in AAAs occurred despite equivalent responses in both genders to AngII-induced increases in blood pressure and atherosclerosis [19]. Initial studies focused on the role of estrogens in providing the protection afforded females in AAA formation. Indeed, administration of 17beta estradiol decreased aneurysm incidence and external aortic diameter in male apoE-/- mice, associated with decreased abundance of many adhesions and chemoattractant molecules [39]. However, in a subsequent study, ovariectomy of female apoE-/- mice had no effect on AngII-induced AAAs [19]. It also failed to influence AngII-augmented atherosclerosis. Conversely, orchidectomy of male apoE-/- mice reduced the incidence of AAAs to a level that was observed in female mice. As another example of the discord in the mechanisms underlying AAAs and atherosclerosis, there was an increase in lesion size in these mice despite the benefit on AAAs. Thus, there are many issues that need to be defined concerning the role of gender in the development of AngII-induced vascular diseases.

RAS and Human AAAs

Genetic associations of the RAS in human AAAs have provided conflicting results. One study has examined the role of the A1166C polymorphism in the 3'-UTR of the AT1 receptor and failed to find an association with AAAs [40]. This study also examined the ACE I/D genotypes. In one study, the DD genotype of ACE I/D polymorphisms was independently related to AAAs. Since the D allele of the ACE gene is associated with increased serum levels of circulating ACE, it was suggested that ACE gene polymorphism may be useful as a marker or predictor of human AAA formation [40]. However, another study failed to find any relationship between ACE I/D polymorphism and AAAs [41]. The controversy between these two ACE polymorphism studies may be partially attributable to different populations and small patient number. In addition, due to the complex characteristics of gene polymorphisms, larger population studies are necessary to define the functional molecular mechanisms of the RAS genes in development of human AAAs.

There are some data from small clinical studies that ACE inhibitors may be beneficial to patients with AAAs. These includes reduced acute vascular events in patients with AAAs [42] and improved survival in AAA patients [43]. More recently, Hackam and colleagues have reported a large population-based case-control study about the influence of ACE inhibition on the risk of aortic rupture [44·]. After analyzing 15,326 patients hospitalized with a primary diagnosis of AAAs, they found that patients receiving ACE inhibitors before admission were significantly less likely to present with aortic rupture. This beneficial effect may be independent of ACE inhibitors' antihypertensive properties because other antihypertensive agents were not associated with a lower risk of AAA rupture. Since a major effect of ACE inhibitors is to reduce synthesis of AngII, this finding is consistent with animal studies that demonstrate the ability to produce AAAs during chronic infusion of AngII [6]. Surprisingly, the beneficial effect of ACE inhibitors was not seen in patients treated with AngII type 1 receptor blockers. However,

this apparent discrepancy probably related to the number of patients taking AT1 receptor blockers in this study (1%). Thus, at present, this observation does not negate an effect for ARB.

The effects of the RAS in AAA development will require completion of a double-blinded prospective randomized clinical trial. For example, such a trial has been designed for determining effects of doxycycline on AAA growth [45]. A challenge in evaluating the efficacy of inhibiting RAS components will be that a substantial number of patients afflicted with AAAs are already prescribed ACE inhibitors or ARBs for other cardiovascular diseases. However, these studies could be accomplished with dose titrations of ACE inhibitors or ARBs, or the use of the newly approved renin inhibitor, aliskiren.

RAS in Ascending Aortic Arch Aneurysms

Patients afflicted with Marfan's syndrome have numerous health issues, but the most life-threatening is the development of aortic arch aneurysms. Marfan's syndrome is a systemic disorder of connective tissues caused by mutations in the fibrillin-1 gene (FBN1), [2]. There are numerous mutations in this gene that probably underlie the variable presentation of this disease. Although fibrillin-1 is an extracellular matrix microfibril, the disease is unrelated to a structural deficiency of this protein, but rather due to its ability to promote excessive activity of transforming growth factor-beta [46·].

Mice that are hypomorphic for fibrillin-1 developed aortic dilations that are associated with elastin fragmentation and macrophage accumulation. Also, transgenic mice that express a common mutant in Marfan's patients, C1039G, developed aortic aneurysms that are localized to the aortic arch [46]. Interestingly, administration of the AT1 receptor antagonist, losartan, completely attenuated the aortic arch pathology that was generated by the expression of the mutant fibrillin-1. No other sartan has been administered to models of aortic arch aneurysms to determine whether this effect is class specific for AT1 receptor antagonism. Additional evidence for a role of the RAS has been provided by the demonstration that chronic infusion of AngII generated a pathology resembling that in the fibrillin-1 C1039G transgenic mice [29].

There is currently scant information on the potential benefit of RAS inhibition on ascending aortic arch aneurysms. Specific genetic associations of Marfan's syndrome have been associated with enhanced expression of ACE [47]. Two recent studies have demonstrated that ACE inhibitors reduced both aortic stiffness and aortic root diameter in patients with Marfan's syndrome [48,49]. A randomized clinical trial is currently ongoing to compare beta adrenoceptor blockade using atenolol, with AT1 receptor antagonism using losartan, in patients with Marfan's syndrome [50·]. The result of this important clinical trial will provide considerable insight into the role of the RAS in ascending arch aneurysms.

Conclusions

There is evolving and consistent evidence in both the basic science and clinical arenas that the RAS is a major contributor to aortic aneurysmal diseases. The availability of mouse models that recapitulate at least some of the major features of these diseases should provide an approach to determine mechanisms. It is hoped that this will facilitate the development and validation of the urgently needed drugs to treat these devastating diseases.

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References

1. Golledge J, Muller J, Daugherty A, Norman P. Abdominal aortic aneurysm. Pathogenesis and implications for management. Arterioscler Thromb Vasc Biol 2006;26:2605–2613. [PubMed: 16973970]
2. Ramirez F, Dietz HC. Marfan syndrome: from molecular pathogenesis to clinical treatment. Curr Opin Genet Dev 2007;17:252–258. [PubMed: 17467262]
3. Daugherty A, Cassis L. Angiotensin II and abdominal aortic aneurysms. Curr Hypertens Rep 2004;6:442–446. [PubMed: 15527688]
4. Daugherty A, Cassis LA. Mouse models of abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2004;24:429–434. [PubMed: 14739119]
5. Daugherty A, Cassis L. Chronic angiotensin II infusion promotes atherogenesis in low density lipoprotein receptor -/- mice. Ann NY Acad Sci 1999;892:108–118. [PubMed: 10842656]
6. Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. J Clin Invest 2000;105:1605–1612. [PubMed: 10841519]
7. Wang YX, Martin McNulty B, Freay AD, et al. Angiotensin II increases urokinase-type plasminogen activator expression and induces aneurysm in the abdominal aorta of apolipoprotein E-deficient mice. Am J Pathol 2001;159:1455–1464. [PubMed: 11583973]
8. Ishibashi M, Egashira K, Zhao Q, et al. Bone marrow-derived monocyte chemoattractant protein-1 receptor CCR2 is critical in angiotensin II-induced acceleration of atherosclerosis and aneurysm formation in hypercholesterolemic mice. Arterioscler Thromb Vasc Biol 2004;24:e174–178. [PubMed: 15331433]
9. Gavrila D, Li WG, McCormick ML, et al. Vitamin E inhibits abdominal aortic aneurysm formation in angiotensin II-infused, apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2005;25:1671–1617. [PubMed: 15933246]
10. Zhou Y, Chen R, Catanzaro SE, et al. Differential effects of angiotensin II on atherogenesis at the aortic sinus and descending aorta of apolipoprotein-E-deficient mice. Am J Hypertens 2005;18:486–492. [PubMed: 15831357]
11. Ayabe N, Babaev VR, Tang Y, et al. Transiently heightened angiotensin II has distinct effects on atherosclerosis and aneurysm formation in hyperlipidemic mice. Atherosclerosis 2006;184:312–321. [PubMed: 16023123]
12. Eagleton MJ, Ballard N, Lynch E, et al. Early increased MT1-MMP expression and late MMP-2 and MMP-9 activity during Angiotensin II induced aneurysm formation. J Surg Res 2006;135:345–351. [PubMed: 16716358]
13. Yoshimura K, Aoki H, Ikeda Y, et al. Regression of abdominal aortic aneurysm by inhibition of c-Jun N-terminal kinase. Nat Med 2005;11:1330–1338. [PubMed: 16311603] . ·· This is the first experimental study to demonstrate the provocative finding that abdominal aortic aneurysms decrease in diameter with mice when administered with a JNK inhibitor.
14. Cao RY, Adams MA, Habenicht AJ, Funk CD. Angiotensin II-induced abdominal aortic aneurysm occurs independently of the 5-lipoxygenase pathway in apolipoprotein E-deficient mice. Prostaglandins Other Lipid Mediat 2007;84:34–42. [PubMed: 17643886]
15. Ahluwalia N, Lin AY, Tager AM, et al. Inhibited Aortic Aneurysm Formation in BLT1-Deficient Mice. J Immunol 2007;179:691–697. [PubMed: 17579092]
16. Vinh A, Gaspari TA, Liu HB, et al. A Novel Histone Deacetylase Inhibitor Reduces Abdominal Aortic Aneurysm Formation in Angiotensin II-Infused Apolipoprotein E-Deficient Mice. J Vasc Res 2007;45:143–152. [PubMed: 17957103]
17. Deng GG, Martin-McNulty B, Sukovich DA, et al. Urokinase-type plasminogen activator plays a critical role in angiotensin II-induced abdominal aortic aneurysm. Circ Res 2003;92:510–517. [PubMed: 12600880]
18. Manning MW, Cassis LA, Huang J, et al. Abdominal aortic aneurysms: fresh insights from a novel animal model of the disease. Vasc Med 2002;7:45–54. [PubMed: 12083734]

19. Henriques TA, Huang J, D'Souza SS, et al. Orchiectomy, but not Ovariectomy, Regulates Angiotensin II-Induced Vascular Diseases in Apolipoprotein E Deficient Mice. Endocrinology 2004;145:3866–3872. [PubMed: 15105380]
20. Saraff K, Babamusta F, Cassis LA, Daugherty A. Aortic dissection precedes formation of aneurysms and atherosclerosis in angiotensin II-infused, apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2003;23:1621–1626. [PubMed: 12855482]
21. Barisione C, Charnigo RJ, Howatt DA, et al. Rapid dilation of the abdominal aorta during infusion of angiotensin II detected by noninvasive high frequency ultrasound. J Vasc Surg 2006;44:372–376. [PubMed: 16890871]
22. Rateri DL, Howatt DA, Xie X, et al. Prolonged infusion of angiotensin II promotes abdominal aortic aneurysm remodeling associated with adventitial macrophage recruitment. Arterioscler Thromb Vasc Biol. 2008 submitted.
23. Powell JT, Brady AR. Detection, management, and prospects for the medical treatment of small abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2004;24:241–245. [PubMed: 14604835] . · An authoritative review of human abdominal aortic aneurysms.
24. Liao S, Miralles M, Kelley BJ, et al. Suppression of experimental abdominal aortic aneurysms in the rat by treatment with angiotensin-converting enzyme inhibitors. J Vasc Surg 2001;33:1057–1064. [PubMed: 11331849]
25. Furubayashi K, Takai S, Jin D, et al. The significance of chymase in the progression of abdominal aortic aneurysms in dogs. Hypertens Res 2007;30:349–357. [PubMed: 17541214]
26. Daugherty A, Manning MW, Cassis LA. Antagonism of AT2 receptors augments Angiotensin II-induced abdominal aortic aneurysms and atherosclerosis. Br J Pharmacol 2001;134:865–870. [PubMed: 11606327]
27. Cassis LA, Rateri DL, Lu H, Daugherty A. Bone marrow transplantation reveals that recipient AT1a receptors are required to initiate angiotensin II-induced atherosclerosis and aneurysms. Arterioscler Thromb Vasc Biol 2007;27:380–386. [PubMed: 17158350]
28. Cassis LA, Helton MJ, Howatt DA, et al. Aldosterone does not mediate angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. Br J Pharmacol 2005;144:443–448. [PubMed: 15655500]
29. Daugherty A, Ravisankar P, Szilvassy SJ, et al. Angiotensin II infusion promotes ascending aortic aneurysms: Attenuation by CCR2 deficiency. Arterioscler Thromb Vasc Biol. 2008 submitted.
30. Gitlin JM, Trivedi DB, Langenbach R, Loftin CD. Genetic deficiency of cyclooxygenase-2 attenuates abdominal aortic aneurysm formation in mice. Cardiovasc Res 2007;73:227–236. [PubMed: 17137566]
31. King VL, Trivedi D, Gitlin JM, Loftin CD. Selective cyclooxygenase-2 inhibition with celecoxib decreases angiotensin II-induced abdominal aortic aneurysm formation in mice. Arterioscler Thromb Vasc Biol 2006;26:1137–1143. [PubMed: 16514081]
32. Zhang LN, Velichko S, Vincelette J, et al. Interferon-beta attenuates angiotensin II-accelerated atherosclerosis and vascular remodeling in apolipoprotein E deficient mice. Atherosclerosis 2007:ePub.
33. Manning MW, Cassis LA, Daugherty A. Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2003;23:483–488. [PubMed: 12615694]
34. Wen J, Wang P, Smith SV, et al. Syndecans are differentially expressed during the course of aortic aneurysm formation. J Vasc Surg 2007;46:1014–1025. [PubMed: 17905554]
35. Jiang F, Jones GT, Dusting GJ. Failure of antioxidants to protect against angiotensin II-induced aortic rupture in aged apolipoprotein(E)-deficient mice. Br J Pharmacol 2007:ePub.
36. Thomas M, Gavrila D, McCormick ML, et al. Deletion of p47 phox attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein E-deficient mice. Circulation 2006;114:404–413. [PubMed: 16864727]
37. Gavazzi G, Deffert C, Trocme C, et al. NOX1 deficiency protects from aortic dissection in response to angiotensin II. Hypertension 2007;50:189–196. [PubMed: 17502491]

38. Wang YX, Martin-McNulty B, da Cunha V, et al. Fasudil, a Rho-kinase inhibitor, attenuates angiotensin II-induced abdominal aortic aneurysm in apolipoprotein E-deficient mice by inhibiting apoptosis and proteolysis. Circulation 2005;111:2219–2226. [PubMed: 15851596]
39. Martin McNulty B, Tham DM, daCunha V, et al. 17 beta-estradiol attenuates development of angiotensin II induced aortic abdominal aneurysm in apolipoprotein E deficient mice. Arterioscler Thromb Vasc Biol 2003;23:1627–1632. [PubMed: 12855485]
40. Fatini C, Pratesi G, Sofi F, et al. ACE DD genotype: a predisposing factor for abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2005;29:227–232. [PubMed: 15694792]
41. Yeung JM, Heeley M, Gray S, et al. Does the angiotensin-converting enzyme (ACE) gene polymorphism affect rate of abdominal aortic aneurysm expansion? Eur J Vasc Endovasc Surg 2002;24:69–71. [PubMed: 12127851]
42. Claridge MW, Hobbs SD, Quick CR, et al. ACE inhibitors increase type III collagen synthesis: a potential explanation for reduction in acute vascular events by ACE inhibitors. Eur J Vasc Endovasc Surg 2004;28:67–70. [PubMed: 15177234]
43. Lloyd GM, Newton JD, Norwood MG, et al. Patients with abdominal aortic aneurysm: are we missing the opportunity for cardiovascular risk reduction? J Vasc Surg 2004;40:691–697. [PubMed: 15472596]
44. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. Lancet 2006;368:659–665. [PubMed: 16920471] . · A case control study using the extensive medical records of the Ontario health system to determine that patients administered with ACE inhibitors had a lesser incidence of abdominal aortic rupture.
45. Thompson RW, Baxter BT. MMP inhibition in abdominal aortic aneurysms. Rationale for a prospective randomized clinical trial. Ann NY Acad Sci 1999;878:159–178. [PubMed: 10415728]
46. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 2006;312:117–121. [PubMed: 16601194] . ·· Creation of a transgenic mouse using a fibrillin-1 mutant causes Marfan's syndrome. Expression of this mutant protein produced extensive aortic dilation that is restricted to the ascending aortic region.
47. Pannu H, Tran-Fadulu V, Papke CL, et al. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. Hum Mol Genet 2007;16:3453–3462.
48. Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. Am J Cardiol 2005;95:1125–1127. [PubMed: 15842990]
49. Ahimastos AA, Aggarwal A, D'Orsa KM, et al. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. JAMA 2007;298:1539–1547. [PubMed: 17911499]
50. Lacro RV, Dietz HC, Wruck LM, et al. Rationale and design of a randomized clinical trial of beta-blocker therapy (atenolol) versus angiotensin II receptor blocker therapy (losartan) in individuals with Marfan syndrome. Am Heart J 2007;154:624–631. [PubMed: 17892982] . ·The design of a clinical trial that could have a major impact on the treatment of individuals afflicted with Marfan's disease.

Table 1

Recent mechanistic studies of AngII infusion-induced AAAs in mice.

Category	Approach	Mouse		Effect on AAAs	Reference
		Strain	Gender		
RAS components	AT1aR -/- : whole body	LDLR -/-	male	↓	[27]
	AT1aR -/- : bone marrow			↔	
	aldosterone	apoE-/-		↔	[28]
	MR antagonism : spironolactone			↔	
Inflammation	CCR2 -/- : whole body			↓	[29]
	CCR2 -/- : bone marrow			↓	[8,29]
	COX-2 -/-	hybrid	NS	↓	[30]
	COX-2 inhibition : celecoxib	apoE -/-	male	↓	[31]
	COX-1 inhibition : SC-560			↔	
	5-LO -/-			↔	[14]
	5-LO inhibition : MK-0591			↔	
	BLT1 -/-		NS	↓	[15]
	IFN-β		male	↔	[32]
Proteases	HDAC inhibition : MCT-1			↓	[16]
	MMP inhibitor: doxycycline	LDLR-/-		↓	[33]
Oxidative stress	$p47^{phox}$ -/-	apoE -/-		↓	[36]
	NOX1 -/-	C57BL/6 (N6)		↓	[37]
	vitamin E	apoE -/-		↓	[9]
	vitamin E and C			↔	[35]
Intracellular signaling	Rho-kinase inhibition : fasudil			↓	[38]
	JNK inhibition : SP600125			↓	[13··]
Hormonal	Orchidectomy			↓	[19]
	Ovariectomy		female	↔	

NS - not stated