

Angiotensin II and Abdominal Aortic Aneurysms

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Abdominal aortic aneurysms (AAAs) have devastating effects on the morbidity and mortality of a large portion of the elderly population. Current therapeutic options for AAAs are limited to surgical approaches, because there are no proven pharmacologic treatments. Recently, there is evolving evidence that angiotensin II (Ang II) participates in the initiation and propagation of AAAs. Animal studies have consistently demonstrated the ability of Ang II to promote the formation of AAAs, although the mechanisms of this effect have not been defined. Further definition of the role of the renin-angiotensin system in AAA formation and progression will identify potential therapeutic strategies for treatment of this disease.

Introduction

Abdominal aortic aneurysms (AAAs) have a devastating, but generally underappreciated impact on health, particularly in groups older than 50 years. This impact will likely increase as the demographics of the United States shifts toward a population of increased age. Current estimates of AAA incidence (approximately 5% incidence in males > 60 years of age) are variable, partially due to the lack of universally accepted definitions of the disease. One criterion for an aneurysm is a permanent dilation of an artery. However, the definition of whether this has reached a disease status is based either on absolute size of the abdominal aorta or the size of this region relative to a segment that is defined as "normal." Consequently, there can be some difference of opinions on what constitutes an aneurysmal aorta. Perhaps a more appropriate index of the impact of AAAs comes from the number of elective surgeries that implant some form of prosthetic graft. Currently, there are more than 40,000 AAA repairs performed each year in the United States.

Therapeutic options for individuals afflicted with AAA are currently limited to surgery. There is considerable

interest in endovascular approaches to AAA repair, but there are still issues in this approach that have hindered its general acceptance [1]. The surgical intervention needs to be optimally timed for maximum benefit. Therefore, patients diagnosed with an AAA are screened at 3- to 12-month intervals. Screening frequency can depend on AAA size at the time of detection and associated risk factors, such as age and male gender [1]. The average yearly expansion rate is in the range of approximately 20 to 40 mm per year; however, this varies greatly between individuals. Elective graft implantation for small aneurysms has no mortality benefit [2]. Therefore, patients are usually screened until the AAA attains a size greater than approximately 5 cm. The increased rupture rate of AAAs larger than 5.5 cm is the most common guide for performing surgery [3].

Currently, there are no proven pharmacologic options to treat AAAs. The absence of effective drug treatments is partially due to the lack of knowledge on the mechanisms responsible for the initiation and propagation of AAAs. As described in this article, there is now considerable experimental evidence that angiotensin II (Ang II) has the ability to generate AAAs in susceptible mouse strains, with sufficient evidence to justify a more in-depth examination of its role in the human disease.

Evidence Linking Ang II to Experimental Aneurysms

Angiotensin II is an octapeptide that has well-known effects on blood pressure and fluid balance. There is now a growing appreciation that Ang II may also directly exert inflammatory effects in promoting cardiac and vascular disease. In the classic pathway of biosynthesis, Ang II is derived from its only known precursor, angiotensinogen, through sequential cleavage by renin and angiotensin-converting enzyme (ACE). Several other enzymes may be involved in the production of Ang II [4]. However, in the context of AAA research, only chymase has been invoked. Like ACE, chymase activity converts Ang I to Ang II.

Indirect evidence that Ang II can alter the integrity of the arterial wall comes from studies in Brown Norway rats. This rat strain has a propensity to rupture the internal elastic lamina that is abrogated by administration of either ACE inhibitors or angiotensin receptor antagonists [5]. Comparable reductions in blood pressure were obtained by administration of the calcium channel antagonists,

mibefradil and amlodipine, but this did not protect from laminal disruption.

More direct evidence for a role of Ang II in the development of AAAs comes from the Tsukuba hypertensive mouse that overexpresses both the human renin and angiotensinogen genes [6]. When fed a salt-loaded diet, these mice exhibit aneurysms and rupture at the aorta in the arch and suprarenal regions.

Additional direct evidence of the role of Ang II in AAA formation was derived from studies in which this peptide was infused into hyperlipidemic mice. Infusions of Ang II into either low-density lipoprotein (LDL) receptor $-/-$ or apolipoprotein E $-/-$ mice led to the occurrence of large AAAs within 1 month of administration [7,8•]. Subsequent studies have demonstrated that hyperlipidemia is not an absolute requirement for the development of Ang II-induced AAAs in mice, but it does enhance the frequency of aneurysmal disease [9]. Although some of the effects of Ang II may be mediated via aldosterone release, infusion of a wide range of aldosterone doses into apolipoprotein E $-/-$ mice failed to generate AAA [10].

The sequential cellular events in the formation of Ang II-induced AAAs have been defined in apolipoprotein E $-/-$ mice [11]. The first demonstrable cellular event in the abdominal region that develops AAA is the medial accumulation of macrophages. This occurs within 3 days of the start of the infusion and is associated with degradation of elastin fibers. Currently, it is not clear whether the macrophage infiltration is responsible for the elastin degradation or vice versa. Overt medial dissection occurs within 10 days. Generally, the adverse effects of this event are constrained by the adventitia. However, in approximately 10% of mice, this leads to death due to retroperitoneal bleeding. There is an intense inflammatory response following the dissection that is probably seeded by the presence of the mural thrombus. This inflammatory response is manifest by the presence of large numbers of macrophages, and B and T lymphocytes. The tissue also remodels with enhanced fibrosis and pronounced neovascularization. At more advanced stages, prominent atherosclerotic lesions occur as defined by lipid-laden macrophages in the intimal area [11]. This sequence of events is summarized in Figure 1. The AAAs formed in these mice display several characteristics present in the human disease, including regions of intact media, fragmented elastin fibers, proteolytic destruction of medial connective tissue, inflammation, and atherosclerosis [12,13]. Definition of the fidelity that this model recapitulates the events in AAAs will require more knowledge of the cellular events in the human disease. Unfortunately, most of the current descriptions of the pathology of human aneurysms are from tissues acquired at end-stage disease.

One aspect of Ang II-induced AAAs that displays similarities to the human disease is its gender preference, with a higher incidence of more severe aneurysms in males compared with females [14]. The higher incidence of AAAs in males is not due to protective effects of endogenous

estrogen in females, because ovariectomy had no effect on AAA incidence or severity. In contrast, orchietomy reduced both the incidence and severity of Ang II-induced AAAs equivalent to that seen in females [15]. Therefore, testosterone appears to promote the formation of AAAs. Although endogenous estrogen in female mice does not appear to regulate AAA formation, the administration of exogenous estrogen to male apolipoprotein E $-/-$ mice decreased the incidence and size of Ang II-induced AAAs [16]. Future studies on the mechanism of testosterone to increase AAA incidence and severity should provide valuable information on this significant risk factor in human AAA.

Modes of Inhibiting Angiotensin II-induced Abdominal Aortic Aneurysms

Angiotensin II exerts many of its biological properties through activation of angiotensin II type 1 (AT1) receptors. Therefore, it was probably not surprising that co-administration of the AT1 receptor antagonist, losartan, ablated the development of Ang II-induced AAAs in apolipoprotein E $-/-$ mice [17]. In mice, there are two subtypes of the AT1 receptor, designated A and B. Although the A subtype is considered to mediate many of the actions of Ang II in mice, there is recent evidence that AT1b receptors are primary mediators of Ang II-induced aortic contractions [18]. However, recent studies demonstrate that whole body deficiency of AT1a receptors ablates Ang II-induced AAA formation [19]. Future studies on the cell type expressing AT1a receptors that is being activated in the development of AAAs will provide interesting insight into the mechanism of this disease.

Stimulation of AT2 receptors can act as a physiologic antagonist to AT1-receptor stimulation [20]. Therefore, some of the benefits of AT1 receptor antagonism may be associated with the increased concentrations of Ang II-stimulating AT2 receptors [21•]. In agreement with this tenet, co-administration of the AT2 receptor antagonist PD123319 augmented the incidence and severity of Ang II-induced AAAs in apolipoprotein E $-/-$ mice [17]. However, in subsequent studies, we were unable to determine any difference in the formation of AAAs when we infused Ang II into apolipoprotein E mice that were AT2-receptor deficient [22]. Furthermore, the administration of PD123319 to LDL receptor $-/-$ mice resulted in increased Ang II-induced AAAs, irrespective of whether the mice were wild type or deficient for AT2 receptors. Therefore, the role of AT2 receptors in Ang II-induced AAAs appears to be equivocal.

Other than Ang II-receptor antagonists, the major efforts in inhibiting Ang II-induced AAAs have been directed at decreasing proteolysis of extracellular matrix. A role of urokinase was implicated by its increased presence in Ang II-induced AAAs [23]. The causal role of this protease in the aneurysmal process was demonstrated in genetically deficient mice in which absence of urokinase

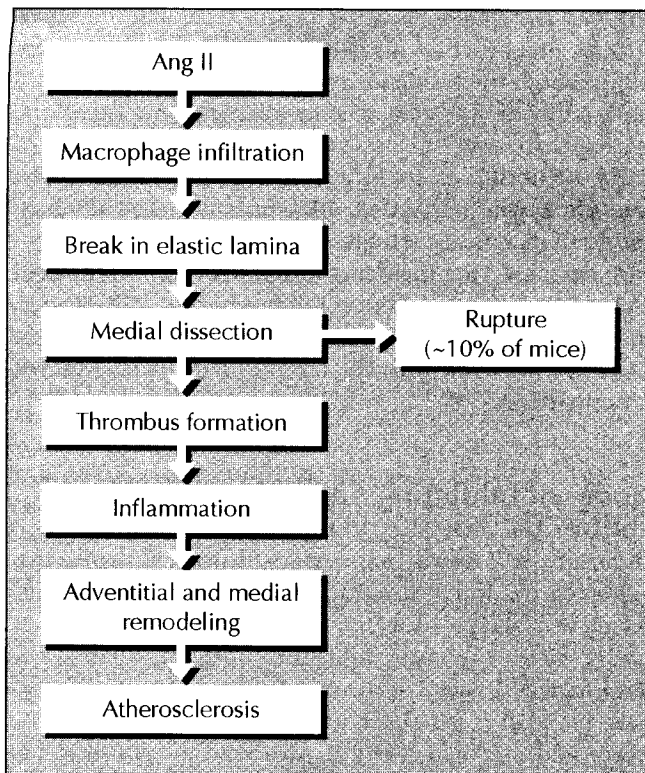


Figure 1. The sequence of cellular events in the evolution of angiotensin II-induced abdominal aortic aneurysms.

virtually ablated Ang II-induced AAAs [9]. Urokinase may be exerting its effects through the activation of matrix metalloproteinases. Consistent with this notion, administration of doxycycline decreased Ang II-induced AAAs in apolipoprotein E^{-/-} mice [24]. Doxycycline is a broad spectrum inhibitor of matrix metalloproteinases. Currently, there are no reports of more specific inhibitors of this class of enzymes. Similarly, there have been no reports of Ang II infusion into mice with genetic deficiencies of specific matrix metalloproteinases.

Recently, it was reported that deficiency of osteopontin decreased Ang II-induced AAA formation in apolipoprotein E^{-/-} mice [25]. Osteopontin was originally identified as a molecule that mediates osteoclast adhesion to mineralized matrix. In addition to this property, it appears to exhibit multiple inflammatory mechanisms by influencing macrophage function. Determination of the mechanisms of this effect may provide further insight into the underlying regulators of AAA formation.

Angiotensin II has also been implicated to participate in animal models of AAAs that are not initiated by Ang II infusion. Elastase infusion into the infrarenal aorta of rats and mice has been a commonly used experimental model of AAAs [26•,27•]. Administration of three different ACE inhibitors had a consistent effect to reduce the medial destruction and inflammation following elastase infusion in mice. Therefore, although Ang II was not involved in the initial insult to the arterial wall, these results are consistent

with a role for Ang II in the subsequent events that led to the overt pathology [28].

Potential Mechanisms of Angiotensin II in Abdominal Aortic Aneurysm Formation

As defined by the sequential cellular events in AAA formation, the generation of AAAs during Ang II infusion is associated with inflammation and medial tissue destruction. Ang II has known effects on inflammatory processes. The role of inflammation has been demonstrated by the partial reduction in Ang II-induced AAAs that occurs in mice that are deficient in CCR2, the chemokine receptor for monocyte chemoattractant protein-1 [29]. A potential source of other chemoattractants is cyclooxygenase II, which has been implicated in the development of AAAs [30,31]. As noted earlier, the smooth muscle-containing media is the site of the initial inflammatory response in AAA formation. Therefore, the ability of Ang II to increase expression of cyclooxygenase 2 in vascular smooth muscle cells is consistent with a role in the disease process [32]. We have noted that Ang II-induced AAAs are reduced in both cyclooxygenase 2-deficient mice or by inhibitors of this enzyme (King, Cassis, Daugherty, and Loftin, Unpublished data). Additional studies are required to determine the spectrum of inflammatory mediators invoked in Ang II-induced AAA.

The medial tissue destruction may be an indirect effect of Ang II via stimulating tissue recruitment of inflammatory cells. Alternatively, it could be exerting an additional effect of stimulating the release of proteolytic enzymes in association with the inflammatory process. However, despite the effects of inhibition of matrix metalloproteinase described earlier, there are limited data that Ang II can stimulate the secretion of enzymes that degrade the extracellular matrix [33]. To the contrary, Ang II can promote fibrotic responses, for example by promoting the secretion of plasminogen activator inhibitor-1 [34]. Therefore, further studies are needed to determine the mechanism of medial destruction that occurs in the early stages of Ang II-induced AAA formation.

Evidence Linking Angiotensin Peptides to Human Abdominal Aortic Aneurysms

The task that lies ahead is to determine whether Ang II-induced AAAs that reproducibly occur in mouse models have relevance to the human disease. Currently, the information linking Ang II and AAAs in humans is sparse. One piece of supporting evidence is the presence of some of the enzymes involved in Ang II production in human aneurysmal tissue, including ACE and chymase [35]. ACE was predominantly present in intimal and medial areas, whereas chymase immunostaining predominated in the media and adventitia. However, arterial pathology tends to be heterogeneous and highly distorted in human aneurysmal tissue, and, therefore, spatial distribution is difficult to

define accurately. Nevertheless, human aneurysmal tissue has an increased ability to generate Ang II via both ACE and chymase, compared with grossly normal segments of human aorta [35].

Gene association studies have noted links between the renin-angiotensin system (RAS) and the development of AAAs, although these have not been consistent. All of the studies have examined the association of ACE polymorphism. The insertion/deletion (I/D) polymorphism of ACE is a designation for the insertion or deletion of a 287 base pair sequence in intron 16. The presence of the insertion leads to decreased ACE activity in plasma. ACE I/D genotype failed to associate with the incidence and rate of AAA expansion in Japanese and British studies, respectively [36,37]. When the subject pool was restricted to normotensive individuals, the DD genotype was found to be more common in AAA patients compared with controls [38]. However, these studies used small numbers of patients, and they need to be substantiated by larger participation of affected individuals.

One method for determining the role of Ang II in the AAA development is to determine the effect of pharmacologic inhibitors on the disease progression. Although these drugs are used widely in cardiovascular disease, the published literature for their effects on AAAs is limited. Although there is no direct evidence to associate a beneficial Ang II-related drug affect to AAA incidence and severity, indirect measures of aortic stiffness, collagen type II turnover, and p22^{phox} expression have implied a benefit of ACE inhibitor or AT1 receptor antagonist administration [39,40]. Based on the ability of AAA tissue to generate Ang II through the chymase pathway, a more effective mode of administration may be through AT1 receptor antagonism.

A definitive approach to clarify the role of Ang II in the development of human AAAs would require a double-blind trial of individuals with nascent AAAs who are treated with a drug that inhibits some aspect of the RAS. A trial design for such a study has already been defined to evaluate the efficacy of matrix metalloproteinase inhibition in AAA [41]. Unfortunately, the common use of both ACE inhibitors and AT1 receptor antagonists in patients with any form of cardiovascular disease will provide a considerable impediment to enrolling a control group for a study. One approach may be to compare the progression of AAAs in patients assigned to "conventional" doses of ACE inhibitors or receptor antagonists versus aggressive therapy with high doses. In addition, a new class of agents, namely renin inhibitors, may offer new insights into the RAS and AAA progression [42].

Conclusions

The mediators of AAA formation have not been defined. However, there is a growing and consistent body of literature demonstrating a role for Ang II in the development of the disease. Given that there is a large pharmacologic

armamentarium to regulate the RAS, therapeutic tools are available to test the hypothesis that inhibition of Ang II actions would have a beneficial effect on AAA formation. Although there are obstacles to defining the importance of the RAS in AAA, the current paucity of medical approaches provides a rationale for investigating this potentially useful drug approach.

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