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Chapter

A New Mouse Model of Aortic Aneurysm Induced by Deoxycorticosterone Acetate or Aldosterone in the Presence of High Salt

Ming C. Gong, Shu Liu and Zhenheng Guo

Abstract

The renin-angiotensin-aldosterone system (RAAS) is implicated in the etiologies of many cardiovascular diseases, including abdominal aortic aneurysm (AAA) and thoracic aortic aneurysm (TAA). In particular, the infusion of angiotensin II (Ang II) in hyperlipidemia mice to induce AAA and TAA has been extensively used in the field, suggesting a critical role of Ang II in aortic aneurysm. In contrast, whether aldosterone (Aldo), a downstream effector of Ang II, is involved in aortic aneurysm is unknown. Here, we describe a new mouse model of AAA and TAA induced by subcutaneous implantation of deoxycorticosterone acetate (DOCA) pellets or infusion of Aldo using osmotic pumps to 10-month-old C57BL/6 male mice in the presence of high salt. The DOCA- or Aldo-salt-induced aortic aneurysm is dependent upon mineralocorticoid receptor activation but independent of Ang II and hypertension and exhibits several unique features that mimic human aortic aneurysm. This review aims to discuss the common animal models of AAA, TAA, and aortic dissection currently studied in the world with the most focus on the DOCA- or Aldo-salt mouse model of aortic aneurysm.

Keywords: aortic aneurysm, angiotensin II, aldosterone, DOCA, high salt, animal model

1. Introduction

An aortic aneurysm is defined as a permanent localized dilation of the aorta with at least a 50% increase in diameter compared with a normal aortic diameter [1]. Aortic aneurysms can be classified according to location as thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). TAA occurs in all-age people without sexual dimorphism and is highly associated with hereditary conditions [2]. By contrast, AAA is typically associated with aging, male sex, smoking, atherosclerosis, and hypertension [3–5]. AAA is the most common form of aortic aneurysm [6], affecting 4–8% of men and 0.5–1.5% of women over the age of 60 and currently accounting for nearly 2% of all deaths in Western countries [2, 3, 7]. Aortic aneurysm is an asymptomatic condition that tends to progress over time with

a high mortality rate (65–85%) if rupture occurs [8]. Unfortunately, repair through open or endovascular surgery is currently the only therapeutic option for aortic aneurysm; no drug has been approved for treatment of this devastating disease [3, 5]. One of the major barriers in the field is a lack of an animal model that fully resembles human aortic aneurysm.

Over the last few decades, a number of rodent models of AAA and TAA have been developed and have been increasingly utilized to be used in understanding the etiology of human AAA and TAA [2, 9–11]. Aortic aneurysm animal models can be classified into three groups [2, 9–11]: (1) genetically predisposed animal models (i.e., fibrillin-1 (FBN1) mutation (Marfan syndrome) mouse model [2, 12]), (2) chemical-induced animal models (i.e., Ang II infusion hyperlipidemia mouse model [9, 13]), and (3) physical or surgical animal models (i.e., decellularized aortic xenograft rat model [10, 14]). Among them, calcium chloride adventitial application model [15, 16], porcine pancreatic elastase (PPE) model [17, 18], and Ang II infusion hyperlipidemia mouse model [13, 19–23] are the commonest animal models currently studied in the world.

One of the fundamental pathological characteristics in human TAA and AAA is thoracic aortic dissection (TAD) and abdominal aortic dissection (AAD), both of which can lead to aneurysmal rupture with high mortality [1–7]. Many genetically predisposed animal models have TAD and AAD (i.e., fibrillin-1 mutation mouse model [2, 12]). Some of the chemical-induced animal models also have TAD and AAD (i.e., fibrillin-1 mutation and Ang II infusion hyperlipidemia mouse models [13, 19–23]). Recently, a new chemical-induced mouse model for more potently induction of TAD and AAD was developed by administration of β -aminopropionitrile monofumarate (BAPN) to mice to inhibit lysyl oxidase (LOX) and/or Ang II infusion [24, 25]. Kurihara et al. demonstrated that BAPN/Ang II induced TAD in 100% of FVB mice [24]. Ren et al. confirmed this finding and further demonstrated that BAPN/Ang II induced TAD and AAD in 75% of C57BL/6J mice, whereas BAPN alone induced TAD in 87% of C57BL/6J [25].

Although no single animal model fully reproduces the histological characteristics and natural history of the human aortic aneurysm, each of these animal models more or less recapitulate human aortic aneurysm and have significantly contributed to the current understanding of clinical management and treatment of patients with AAA and TAA [2, 9–11]. Several clinical trials have begun enrollment to examine whether angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) are effective in the treatment of human aortic aneurysm. However, the results from these clinical trials are inconsistent and disappointing: either effective [26], no effect [27], or, even worse [28], indicating that the current understanding about the etiologies of aortic aneurysm is limited and additional unknown signaling and mechanism may underlie aortic aneurysm and account for the failure of these clinical trials.

In sharp contrast to the well-established role of Ang II in aortic aneurysm [13, 19–23], little is known about the role of aldosterone (Aldo) in aortic aneurysm. Aldo is a steroid hormone primarily synthesized and released by the adrenal glands. Aldo is a downstream effect of Ang II and is well recognized for its critical role in renal sodium reabsorption and water retention and consequently extracellular volume and blood pressure [29, 30]. Accumulated data over the last decade, however, demonstrate that Aldo not only acts on the kidney but also targets many other organelles, including those in the cardiovascular system, where it is critically involved in diverse pathophysiological processes [31–33].

Several lines of clinical study implicate Aldo signaling in aortic aneurysm. First, individual case reports demonstrated that primary hyperaldosteronism is associated with aortic dissection [34–36]. Second, a retrospective study demonstrated that

aldosteronism is associated with high morbidity and mortality from the early onset of hemorrhagic stroke and ruptured intracranial aneurysms [37]. Third, a few small studies have shown an association between obesity and increased levels of Aldo [38] and increased AAA [39]. Finally, perhaps also the most compellingly, an analysis of drug modulation of AAA development through 25 years of surveillance in 1269 patients demonstrated a strong association between mineralocorticoid receptor (MR; also known as Aldo receptor) blockers and slowed AAA progression [40]. However, whether Aldo causes aortic aneurysm is unknown.

By incidence, we discovered that administration of deoxycorticosterone acetate (DOCA) to 10-month-old C57BL/6 male mice caused substantial animal death in the presence of high salt due to aortic aneurysmal rupture. A subsequent series of substantial studies demonstrated that activation of MR by either implantation of DOCA pellet or infusion of Aldo in 10-month-old C57BL/6 male mice was sufficient to induce AAA and TAA formation and aneurysmal rupture in the presence of high salt [41–43]. Recently, we published the detailed methodology on how to implant DOCA pellet or Aldo pumps to induce aortic aneurysm [44]. Here, we will focus on the significant novel finding of this new AAA mouse model, highlight its unique features that mimic human aortic aneurysm, and discuss its significance and potential impact on the current understanding, diagnosis, and treatment of human aortic aneurysm.

2. Development of a new mouse model of aortic aneurysm induced by DOCA- or Aldo-salt

2.1 Discovery of DOCA-salt mouse model of aortic aneurysm by accident

In an independent pilot study using 10- to 12-month-old C57BL/6 male mice to investigate DOCA-salt-induced hypertension, we unexpectedly observed that many mice died from AAA rupture. We were intrigued by this observation since it raised the possibility that activation of the MR by DOCA can cause AAA in the presence of high salt. Given that administration of DOCA and salt to mice or rats have been used extensively as an experimental model of low-renin hypertension [45], it was surprising that DOCA-salt-induced AAA has not been reported in previous studies. While the exact reasons for this discrepancy are unclear, our results suggest that the age of mice (i.e., 10-month old *vs.* 10-week old) may be critical for DOCA and salt to induce AAA (see below).

2.2 Both DOCA and high salt are required to induce aortic aneurysm

To verify our pilot studies and define whether DOCA, salt, or both is critical for DOCA-salt-induced aortic aneurysm, 10-month-old C57BL/6 male mice received DOCA alone (subcutaneous implantation of DOCA pellets; 50 mg, 21-day release; Innovative Research of America, USA), salt alone (drinking water containing 0.9% NaCl plus 0.2% KCl), DOCA and salt, or no treatment (controls). We used C57BL/6 mice because C57BL/6 mice are more susceptible to chemical (i.e., BAPN/Ang II)-induced TAD, AAD, and aneurysmal rupture than other strains of mice (i.e., FVB mice) [24, 25]. We used 10-month-old rather than 10-week-old mice because we found that DOCA- or Aldo-salt-induced aortic aneurysm were aging dependent [41, 43]. We used male mice rather than female mice because DOCA- or Aldo-salt-induced aortic aneurysm has sex difference (unpublished data). All mice were euthanized 3 weeks after treatment.

We used three different approaches to quantify DOCA-salt-induced aortic aneurysm. First, the maximal intraluminal diameters of abdominal aortas were

quantified *in vivo* by a high-resolution ultrasound imaging system (Vevo 2100, Visualsonics, Toronto, Canada). The results showed that both DOCA and salt but not DOCA or salt alone could potentially induce abdominal aortic dilation relative to the control [41]. Second, the maximal external diameters of isolated abdominal and thoracic aortas were quantified *ex vivo* by Nikon SMZ800 Stereo Microscope with a digital camera and NIS-Elements software. Consistently with the ultrasound data, both DOCA and salt but not DOCA or salt alone significantly increased external diameters of abdominal and thoracic aortas relative to the control [41].

Third, we calculated the incidence of DOCA-salt-induced AAA, TAA, and aneurysmal rupture based on the definition that AAA or TAA has at least a 50% increase in diameter compared with the normal diameter of the aorta [1]. Of the 45 mice treated with DOCA-salt, 28 mice developed AAA (62%), 22 mice developed TAA (42%), and 8 mice died of aortic aneurysmal rupture (18%). In contrast, no AAA, TAA, or aortic aneurysmal rupture was observed in control, DOCA, or salt alone. Interestingly, AAA was only found in the suprarenal abdominal aorta, which is similar to that in the Ang II AAA mouse model [13], whereas TAA was mostly associated with AAA and was mostly observed in the descending thoracic aorta, indicating that TAA is likely derived from AAA.

2.3 Infusion of mice with Aldo can also induce aortic aneurysm in the presence of high salt

Since DOCA is a synthetic MR agonist, we wondered whether Aldo, a physiologic ligand of MR in our body, could induce aortic aneurysm in the presence of high salt. To define the concentration of Aldo that is sufficient to induce aortic aneurysm in the presence of high salt, 10-month-old C57BL/6 male mice were infused with three different doses of Aldo (200, 500, and 700 $\mu\text{g}/\text{kg}/\text{day}$) for 4 weeks. Aldo was delivered to mice via subcutaneous implantation of osmotic minipump (Alzet model 2004; DURECT, USA) containing Aldo solubilized in 50% DMSO. All groups of mice were treated for 4 weeks.

Infusion of mice with all three doses of Aldo was very similar to implantation of mice with DOCA pellets and markedly increased maximal intraluminal and external diameters of suprarenal abdominal aortas compared to the control mice (without treatment). Similarly, infusion of mice with all three doses of Aldo is also similar to implantation of mice with DOCA pellets and potentially induced AAA (over 58%), TAA (over 42%), and aneurysmal rupture (over 25%) compared to the control mice. These data demonstrated that the infusion of mice with 200 $\mu\text{g}/\text{kg}/\text{day}$ Aldo is sufficient to induce AAA in the presence of high salt.

We measured the plasma Aldo concentrations by a commercial EIA kit (Enzo Life Science, USA) 4 weeks after Aldo and salt administration. We found that plasma Aldo concentrations were elevated in a dose-dependent manner. Of note, infusions of mice with 200 $\mu\text{g}/\text{kg}/\text{day}$ Aldo resulted in plasma Aldo concentrations to ~ 10 nM, which could be seen in some human diseases such as congestive heart failure and primary aldosteronism [31, 46, 47]. These results indicate that the Aldo-salt AAA mouse model is a physiopathological model that mimics human diseases rather than a pharmacological model that would cause concerns due to the use of high doses of reagent.

2.4 DOCA-salt-induced aortic aneurysm is independent of Ang II

Although systematic plasma renin and Ang II concentrations are suppressed in animals administered with DOCA and salt [45], local aortic Ang II concentration can be increased due to activation of vascular RAAS, which was thought to be of

pathophysiological relevance to the development of atherosclerosis [48]. Moreover, there is a synergistic interaction between Ang II and Aldo in VSMCs [49, 50]. Therefore, it is interesting to investigate whether DOCA-salt-induced aortic aneurysm is dependent upon Ang II. To address this important question, 10-month-old C57BL/6 male mice were treated with either an ACE inhibitor (enalapril) or an ARB (losartan) before (1 week) and after (4 weeks) DOCA-salt administration. As expected, enalapril or losartan effectively decreased blood pressure, but enalapril or losartan had little effect on the DOCA-salt-induced aortic dilation, aortic aneurysm formation, and aneurysmal rupture [41]. These results demonstrate that the DOCA-salt-induced aortic aneurysm is independent of Ang II thus provide an alternative mouse model of aortic aneurysm for investigators in the field who need an Ang II-independent mouse model to verify their key findings.

2.5 Activation of MR is a prerequisite for DOCA- or Aldo-salt to induce aortic aneurysm

To define the role of MR in DOCA- or Aldo-salt-induced aortic aneurysm, we treated 10-month-old C57BL/6 male mice with an MR antagonist eplerenone 1 week before and 4 weeks after Aldo-salt administration [41]. Eplerenone (Pfizer, USA) was delivered by feeding mice with custom diets (chow supplemented with eplerenone at 2.5 mg/g, Research Diets, Inc., USA). In contrast to the minimal effect of blocking Ang II with enalapril or losartan, treatment of mice with eplerenone completely abolished Aldo-salt-induced aortic dilation, AAA formation, and aortic aneurysmal rupture [41]. A similar but less potent effect on DOCA-salt-induced AAA was also found in mice treated with spironolactone [41]. These results suggest that activation of MR by DOCA or Aldo is a prerequisite for DOCA- or Aldo-salt to induce aortic aneurysm.

2.6 DOCA-salt induces aortic aneurysm independent of increased blood pressure

Administration of DOCA and salt to mice or rats has been used in the field to induce hypertension [45]. Hypertension is recognized as a potential risk factor for aortic aneurysm [3–5]. Thus, it is important to determine whether hypertension contributes to DOCA-salt-induced aortic aneurysm. Blood pressure was measured using a noninvasive tail-cuff system (Coda 6; Kent Scientific Corp., USA). As expected, administration of DOCA or Aldo plus salt to 10-month-old male mice increased both blood pressure and external diameters of the abdominal aorta [41, 43]. However, there was no correlation between blood pressure increase and external diameters of abdominal aorta after DOCA-salt treatment. Similarly, there was also no difference in blood pressure between the mice with aortic aneurysm and the mice without aortic aneurysm. Moreover, treatment of mice with ACE inhibitor enalapril or ARB losartan effectively decreased blood pressure, but both enalapril and losartan had little effect on DOCA-salt-induced aortic aneurysm. Thus, we concluded that DOCA-salt induces aortic aneurysm independent of increased blood pressure. This conclusion is consistent with that in the Ang II infusion AAA mouse model [19].

2.7 Vascular pathology of DOCA- or Aldo-salt induced aortic aneurysms

Human aortic aneurysm is characterized by elastin and collagen degradation, matrix metalloproteinase (MMP), upregulation, inflammatory cell infiltration, vascular smooth muscle cell degeneration, and oxidative stress [51]. To investigate

whether DOCA- or Aldo-salt-induced aortic aneurysms have these pathologic features, paraffin-embedded aortic cross-sections were subjected to Elastic-Van Gieson staining of elastin. Interestingly, elastin degradation was only observed in AAA induced by DOCA- or Aldo-salt [41, 43]. Immunocytochemistry studies revealed that MMP2, MMP9, F4/80 (macrophages), Ly6B2 (neutrophils), caldesmon (smooth muscle cells), terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL; apoptosis), and dihydroethidium (DHE; oxidative stress) were increased in aortas with AAA compared with that in control aortas [41, 43].

In agreement with these immunocytochemical studies, we determined mRNA expression of several inflammatory genes, including vascular cell adhesion molecule 1 (Vcam-1), chemokine (C-C motif) ligand 2 (Ccl2, also known as MCP-1), tumor necrosis factor (Tnf), and Ncf1 (also known as p47^{phox}) in both abdominal and thoracic aortas from mice-administrated DOCA-salt or control mice. We found that Vcam-1, Ccl2, Ncf1, and Tnf were all markedly upregulated in thoracic aortas from mice-administrated DOCA-salt compared to control mice. Interestingly, Vcam-1, Ccl2, and Ncf1, but not Tnf, were also significantly upregulated by DOCA-salt in abdominal aorta from mice-administrated DOCA-salt compared to control mice [41, 43].

2.8 Unique features of the DOCA- or Aldo-salt mouse model of aortic aneurysm

The DOCA- or Aldo-salt mouse model exhibited several unique features that may be relevant to the human aortic aneurysm. First, DOCA- or Aldo-salt-induced aortic aneurysm required to use 10-month-old mice [41, 43] rather than 10-week-old mice (mostly used by the Ang II AAA mouse model [13, 19–23] and other chemical-induced mouse models [17, 18, 24, 25]). Given the fact that human AAA occurs in old peoples [2, 3, 7], the DOCA- or Aldo-salt mouse model of aortic aneurysm may more resemble human AAA than other chemical-induced aortic aneurysms in this regard. Second, DOCA- or Aldo-salt-induced aortic aneurysm used wild-type C57BL/6 mice [41, 43] rather than hyperlipidemia mice (i.e., apolipoprotein E-deficient (ApoE^{-/-}) used by Ang II infusion mouse models [13, 19–23]), thus avoiding the potential confounding effects of hyperlipidemia on aortic aneurysm. Third, using Aldo, a physiological agonist of MR, rather than chemicals (i.e., calcium chloride or pancreatic elastase) to induce aortic aneurysm, highlights its potential role in the etiology of aortic aneurysm. Moreover, the plasma concentration of Aldo in mice infused with Aldo [41] could be seen in human congestive heart failure and primary aldosteronism [31, 46, 47], suggesting that the Aldo-salt AAA mouse model is a pathological model rather than a pharmacological model that would cause concerns due to the use of high doses of reagent. Finally, high salt intake was required for DOCA to induce aortic aneurysm [41], indicating that high salt intake may be a new risk factor for the development of human AAA.

2.9 Significance and potential impact of the DOCA- or Aldo-salt mouse model of aortic aneurysm

We described a new mouse model of aortic aneurysm induced by administration of MR agonist DOCA or Aldo plus high salt to 10-month-old male mice and provided compelling preclinical evidence that reveals a previously unrecognized, but potentially significant, role of Aldo, MR, and high salt in the pathogenesis of AAA. It is worth pointing out that this new mouse model of aortic aneurysm could be used as a platform to study intervention including medication (i.e., we have tested the effect of ACE inhibitor (enalapril), ARB (losartan), and MR antagonist (eplerenone and spironolactone) [41]). It is also worth pointing out at least three

significance and potential impact of the DOCA- or Aldo-salt mouse model of aortic aneurysm on the current basic research and clinical practice on the etiology, clinic diagnosis, evaluation, and treatment of AAA.

First, in agreement with the pivotal role of Aldo in cardiovascular diseases (i.e., hypertension and heart failure) [31, 32, 46], our studies highlight a potentially important but previously unrecognized role of Aldo in the etiology of human aortic aneurysm. Our studies suggest that increased plasma concentration of Aldo may be a new risk factor for human aortic aneurysm or may serve as a new plasma bio-marker for evaluation of aortic aneurysm progression.

Second, it is well recognized that unfavorably excessive dietary sodium intakes remain prevalent around the world and are associated with an increased risk for cardiovascular diseases including hypertension, stroke, coronary heart disease, heart failure, and renal disease [52–54]. However, it is unknown that excessive dietary sodium intake may also be detrimental to the aorta with respect to aortic aneurysm. Our finding that excessive dietary sodium intake was essential for MR agonist to induce aortic aneurysm in mice suggests that excessive dietary sodium intakes may also be implicated in the etiology of human aortic aneurysm. In agreement with our findings, it was recently reported that high salt intake was associated with an increased prevalence of AAA in older men [55]. Moreover, our findings indicate that lifestyle change such as reduction of dietary sodium intakes may be effective to prevent old people from the development and progression of aortic aneurysm.

Third, given the fact that currently there is no approved drug for treatment of AAA, our studies suggest that spironolactone and eplerenone, two clinically approved drugs that have been used for the treatment of human heart failure and essential hypertension [56], may also be effective in the treatment of human aortic aneurysm. Recently, a proof-of-concept randomized controlled clinical trial has been initiated based on our findings and is currently going on in Australia, which aims to test the effect of eplerenone on the progression of AAA (<https://clinicaltrials.gov/ct2/show/study/NCT02345590>).

3. Conclusions

1. Subcutaneous implantation of MR agonist DOCA pellets to 10-month-old C57BL/6 male mice can potently induce aortic aneurysm formation and rupture in the presence of high salt. Both DOCA and salt, but not DOCA or salt alone, are required to induce aortic aneurysm formation and rupture in mice.
2. Infusion of 10-month-old C57BL/6 male mice by subcutaneous implantation of osmotic pumps to release Aldo to a pathological level can also induce aortic aneurysm formation and rupture, suggesting that increased plasma concentration of Aldo may be implicated in the etiology of human aortic aneurysm.
3. DOCA- or Aldo-salt-induced AAA mimics human AAA with respect to elastin degradation, MMP activation, inflammatory cell infiltration, smooth muscle cell degeneration, and oxidative stress.
4. Treatment of mice with ACE inhibitor enalapril or an ARB losartan has little effect on DOCA-salt-induced aortic aneurysm, suggesting that DOCA-salt-induced aortic aneurysm is independent of Ang II.
5. Treatment of mice with MR antagonist spironolactone and eplerenone effectively abolishes or diminishes DOCA- or Aldo-salt-induced aortic aneurysm,

suggesting that activation of MR is a prerequisite for DOCA- or Aldo-salt to induce aortic aneurysm, and more importantly, spironolactone and eplerenone, two clinically approved drugs, may also be effective for the treatment of some aortic aneurysm.

6. There is no correlation between blood pressure and aortic dilation or AAA formation in the DOCA- or Aldo-salt mouse model of aortic aneurysm, suggesting that DOCA-salt induces AAA independent of increased blood pressure.

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Conflict of interest

The authors have no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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