Aortic aneurysm and aortic dissection are important causes of mortality, which are principally managed by surgical interventions.1,2 The absence of specific medications which can limit the complications of these important aortic pathologies has stimulated an intense interest in studying the mechanisms underlying these diseases.1,3 A major focus of these studies has been the renin–angiotensin system. Angiotensin II has been linked to aortic aneurysm and dissection on the basis of evidence from a range of studies. In >100 studies in specific mice species (eg, apolipoprotein E–deficient mice), it has been shown that angiotensin II infusion stimulates aortic aneurysm and dissection formation and rupture.4 Such angiotensin II–induced aneurysms have some features typically found in human abdominal aortic aneurysms, including upregulation of proinflammatory cytokines and matrix metalloproteinases and marked influx of inflammatory cells.5 The concentration of a variety of angiotensin II–producing enzymes, including angiotensin–converting enzyme (ACE) and chymase, is increased in biopsies of human aortic aneurysm.5 In some rodent model studies investigating angiotensin II using angiotensin type I receptor (ATR1) blockers or ACE inhibitors has been successful in limiting aneurysm development or progression.1,3 Genetic polymorphisms in the ATR1 have been associated with human aortic aneurysm.6 On the basis of these and other data, several trials are underway to assess the efficacy of ATR1 blockers and ACE inhibitors in limiting progression of thoracic and abdominal aortic aneurysm.2

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One of the many effects of angiotensin II is to stimulate release of the mineralocorticoid aldosterone from the adrenal cortex. In the current issue of *Arteriosclerosis, Thrombosis and Vascular Biology*, Liu et al7 describe studies investigating the role of the mineralocorticoid receptor (MR) in aortic aneurysm and dissection development in C57BL/6 male mice.7 There were 4 key findings of the study. First, administration of a MR agonist plus salt induced aortic aneurysm and dissection. Second, the aneurysms had some histological features similar to human aortic aneurysm, including elastin degradation, elevated matrix metalloproteinases activity, vascular smooth muscle cell apoptosis, macrophage and neutrophil infiltration, and upregulation of a range of inflammatory and oxidative stress markers. Histological evidence of aortic dissection was also demonstrated in 40% of the mice. Third, MR antagonism attenuated MR agonist and salt-induced aneurysm formation. Fourth, there was no association between the rise in blood pressure induced by MR and salt and the size or incidence of aneurysm development. Administration of an ATR1 blocker or ACE inhibitor did not influence aneurysm incidence despite lowering of blood pressure.

Previously published data also support the role of the MR in aneurysm formation. Kanematsu et al8 reported that administration of the MR agonist deoxycorticosterone acetate plus 1% salt (or angiotensin II) and a lysyl oxidase inhibitor (which blocks cross-linking of elastin and collagen) promoted aortic aneurysm formation in C57BL/6 mice. Tada et al9 reported that a MR antagonist inhibited cerebral aneurysm formation in a rat model of hypertension and salt administration. Similar to the current study they also reported that a MR agonist plus salt promoted cerebral aneurysm formation. This effect was associated with upregulation of inflammatory, oxidative stress, and renin–angiotensin system markers. A previous ultrasound surveillance study involving 1269 patients with abdominal aortic aneurysm found that the prescription of potassium sparing diuretics (presumed to be mainly the MR antagonist spironolactone) was associated with a reduced rate of aneurysm expansion, although this association was lost after adjusting for other medications.10 Hyperaldosteronism has also been associated with cerebral aneurysm formation in patients.11

Based on the above data it is tempting to conclude that aldosterone is the primary effector of angiotensin II in stimulating aortic aneurysm and dissection in mice models and thus a possible target for drug therapy. A previous study, however, suggested that the MR antagonist spironolactone did not inhibit angiotensin II–induced aneurysms in apolipoprotein E–deficient mice, although the drug was administered at approximately a quarter of the dose used in the study of Liu et al.7,12 It is also important to note that MR agonists alone, in the absence of salt administration, do not induce aneurysm formation.7,12 It is thus currently unclear what relative contribution aldosterone makes to the ability of angiotensin II to promote aneurysm. Available evidence from mouse models suggests independent effects of both angiotensin II and aldosterone in promoting pathological changes implicated in aortic aneurysm and dissection, including promotion of inflammation, oxidative stress, and matrix degradation (Figure). A major effect of MR stimulation is to promote retention and ingestion of sodium with resultant expansion of the
Figure. Simplified scheme of how angiotensin II and aldosterone might combine to promote pathological changes, leading to aortic aneurysm and dissection. VSMCs indicates vascular smooth muscle cell. NA indicates sodium.

extracellular fluid volume. Coadministration of salt seems critical in the ability of MR agonists to promote aneurysm.7–9 Salt intake has been linked with intracranial aneurysm rupture in experimental models and patients.10–11 Studies in rodent models suggest that salt retention increases blood pressure and also promotes systemic inflammation.12 Although blood pressure has not been correlated with aneurysm severity, many rodent models of aneurysm require some degree of hypertension, suggesting hemodynamic stress plays some role in producing the dissection which is believed to precede aneurysm formation in these mice models. It is likely that the renin–angiotensin system promotes aortic aneurysm and dissection through several mechanisms summarized in the Figure. The relative importance of these is hard to be clear on at this stage and likely depends on the animal model studied. Ultimately, the most important unresolved question is how effective is blockade of the renin–angiotensin system in limiting complications of human aortic aneurysm and dissection. Evidence on this will need to await the completion of current trials studying ATR1 blockers and ACE inhibitors.3 The excellent study by Liu et al3 suggests that MR antagonists are another group of agents which should be considered for such trials. These agents have previously been shown to be of benefit in heart failure patients already prescribed angiotensin II–inhibiting medication, suggesting that they may be feasible to study in abdominal aortic aneurysm patients who are frequently already prescribed ATR1 blockers or ACE inhibitors.12 The study of Liu et al3 also identifies a further rodent model in which mechanisms relevant to aortic aneurysm and dissection can be studied. Ultimately, whether findings from these rodent models will translate into new therapies for patients remains to be seen.3

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References

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