Aldosterone
Villain or Protector?

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During the past decade, there has been heightened interest in aldosterone as a cardiovascular risk factor, fueled by studies documenting its effects on tissues other than epithelial cells. Of particular interest is the role of aldosterone in exacerbating vascular injury. It is likely that the mechanisms mediating the vascular effects of aldosterone differ from its effects on epithelial cells, eg, the renal collecting tubule. For more than a quarter of a century, it also had been assumed that the primary mechanism of aldosterone was mediated by activation of the mineralocorticoid receptor (MR), which in turn increased transcription of MR-responsive genes.

Recently, it has been documented that aldosterone can produce rapid cellular responses—MR-mediated increases in phosphorylation of transduction factors, eg, extracellular signal regulated kinase 1 and 2 (ERK1/2), protein kinase C (PKC), and endothelial nitric oxide synthase (eNOS), and changes in intracellular calcium and hydrogen ions—in addition to its traditional genomic responses. Sometimes these rapid effects are called “nongenomic.” However, it is likely that even the “rapid” actions of aldosterone can lead to genomic effects. Thus, we will use the terms “rapid” and “genomic” to contrast 2 major mechanisms of action of aldosterone.

These rapid effects may be beneficial or detrimental depending on the environment in which aldosterone is acting. For example, phosphorylation of eNOS in endothelial cells leading to increased NO production and vasodilatation would likely be beneficial in an environment where there is decreased perfusion to a vital organ. Activation of vasoconstriction through increases in cytosolic calcium or phosphorylation of ERK1/2 and PKC would be beneficial in hypotension secondary to injury. However, activation of these latter factors would be detrimental in a patient with congestive heart failure or hypertension. It is important to emphasize that genomic actions of aldosterone may have a similar balance of positive and negative effects as noted above for its rapid actions. For example, stimulation by aldosterone of epithelial sodium channels increases sodium absorption, which is beneficial in volume depleted individuals but not in hypertensive patients. Thus, whether aldosterone is a villain or protector depends on the balance of endogenous and exogenous factors.

Support for this concept comes from both clinical and experimental studies. For example, in rodents, treatment with angiotensin II and an NO synthase inhibitor causes vascular, cardiac, and renal injury, which is prevented by blockade of the MR. However, this injury also is prevented by dietary sodium restriction suggesting that sodium restriction affects the balance of positive and negative effects induced by aldosterone. Mechanistically, on a liberal sodium intake, acute aldosterone administration reduces phosphorylated eNOS (a vascular protector) and increases phosphorylated ERK1/2 and PKC (vascular villains). In contrast, dietary sodium restriction increases phosphorylated eNOS and decreases phosphorylated ERK1/2 and PKC basally, and minimizes or reverses their responses to acute aldosterone administration.

In vitro studies also document beneficial and adverse effects of aldosterone and further extend this concept to include variable effects depending on the cell studied. In rabbit preglomerular arterioles, aldosterone causes rapid dose-dependent vasoconstriction by activation of inositol 1,4,5-triphosphate and PKC pathways. However, this vasoconstriction is counterbalanced by aldosterone increasing endothelium-derived NO. Furthermore, in potassium-induced vasoconstriction, only the vasodilator effects of aldosterone are apparent. In rat aortic rings, aldosterone rapidly attenuates phenylephrine-mediated vasoconstriction via a phosphatidylinositol 3-kinase–dependent increase in NO in endothelial cells. However, in endothelium-denuded ring segments, aldosterone enhances phenylephrine-mediated vasoconstriction. In addition to these rapid effects of aldosterone modifying vascular function, aldosterone has long-term (genomic) effects. For example, in cultured human umbilical vein endothelial cells, 16-hour exposure to aldosterone increases reactive oxygen species production and reduces vascular endothelial growth factor–induced eNOS phosphorylation. Both effects are abolished by the MR antagonist eplerenone.

Confirmatory studies of these mechanistic hypotheses in humans have been limited. To assess mechanisms of the effects of aldosterone on the vasculature, the most extensively studied vascular bed has been the forearm. Support for a negative effect of aldosterone on this bed comes from studies reporting that chronic MR blockade in patients with congestive heart failure improves forearm blood flow response to acetylcholine and NO bioavailability. The 3 studies in healthy humans, however, have reported conflicting results. Farquharson et al demonstrated that an intravenous infusion...
of aldosterone (12 pmol/min per kg for 240 minutes—a substantially smaller dose than that achieved in the other 2 studies) reduced forearm blood flow response to acetylcholine (endothelium dependent vasodilation) as compared with placebo, but did not affect sodium nitroprusside-induced vasodilation (endothelium independent vasodilation) or noradrenaline- or angiotensin II–induced vasoconstriction. These results suggest that aldosterone impairs endothelium-dependent vasodilation and has no effect on endothelium-independent vasodilation.

Nietlispach et al in this issue of Hypertension report that intraarterial infusions of aldosterone (55 pmol/1000 mL per min for 100 minutes—achieving levels between 80 and 100 ng/dL) or oral fludrocortisone (0.3 mg/d for 2 weeks—three times higher than replacement levels) have no effect on forearm blood flow alone, enhance both acetylcholine- and sodium nitroprusside–induced vasodilation, increases phenylephrine-induced vasodilation, decreases sodium nitroprusside–induced vasodilation, and chronically, but not acutely, enhance NG-monomethyl-L-arginine (L-NMMA; an inhibitor of NO synthesis)-mediated reduction in nitroprusside-induced vasodilation, increases phenylephrine-induced vasoconstriction, and enhances L-NMMA reduction in forearm blood flow. These results suggest that aldosterone, acutely and chronically, has beneficial effects on both endothelium dependent and independent vasodilation.

Schmidt et al report that an intraarterial infusion of aldosterone (1400 pmol/min for 30 minutes—a substantially greater dose than in either of the other 2 studies, but shorter duration) increases forearm blood flow, has no effect on acetylcholine-induced vasodilation, decreases sodium nitroprusside-induced vasodilation, increases phenylephrine-induced vasoconstriction, and enhances L-NMMA reduction in forearm blood flow. These results suggest that aldosterone has no beneficial effects on the forearm vasculature.

It is unclear how to explain these differing results except by differences in dose, duration of treatment, or route of administration. Further, whether there is a beneficial or deleterious effect of aldosterone on the vasculature in vivo is uncertain because of four confounders. (1) Because MR antagonists were not used in any study, it is uncertain whether the effects of aldosterone were mediated by MR. (2) These results fail to explain how dietary sodium restriction is beneficial to the vasculature despite increasing aldosterone to the range achieved by 2 of the 3 studies. (3) In the chronic study by Nietlispach et al, potassium levels decreased and blood pressure rose, both of which may modify vascular function independent of aldosterone, potentially adversely. However, despite these changes in potassium and blood pressure, chronic fludrocortisone treatment improved vascular function. In the acute studies it is unlikely that either potassium levels or blood pressure changed. However, even a short infusion of aldosterone could cause shifts in intracellular potassium. (4) Even though all 3 studies were designed to assess rapid versus genomic effects of aldosterone, it is uncertain that any achieved this goal. For example, Nietlispach et al report that the vascular effects of an acute (presumably rapid nongenomic) aldosterone infusion are similar to those observed with 2 weeks of therapy (likely genomic).

In conclusion, aldosterone has both acute and chronic effects on a variety of target tissues. From the in vitro studies, depending on what tissue is studied, the actions of aldosterone could be beneficial (release of NO by endothelium) or detrimental (activating vasoconstrictor transduction mechanisms in vascular smooth muscle). In the normal animal or subject, the beneficial and detrimental effects are likely balanced to maintain a healthy vasculature. However, when the vasculature is damaged as occurs in congestive heart failure, hypertension, or diabetes, the presumed protective advantage of aldosterone is lost, resulting in its prominent role in vascular damage and organ dysfunction. Finally, it remains to be proven whether the effects on the forearm vasculature are representative of what would be observed in other vascular beds, such as the heart, kidney, and brain.

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**References**


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