Editorial Commentary

The Many Targets of Aldosterone

Ernesto L. Schiffrin

In the current issue of Hypertension, Oberleithner et al\(^1\) demonstrate a new effect of aldosterone acting via mineralocorticoid receptors to stimulate water entry into human endothelial cells. Using atomic force microscopy, these authors show that cultured human umbilical vein endothelial cells respond to aldosterone with sodium and water entry (they swell) and this can be blocked by a mineralocorticoid receptor blocker (spironolactone). Swollen aldosterone-treated endothelial cells shrink when micromolar concentrations of amiloride are applied, concentrations at which amiloride does not inhibit the sodium-proton exchanger. The authors report they already showed that cariporide, a selective inhibitor of the sodium-proton exchanger, does not affect aldosterone-induced endothelial cell swelling.\(^1\) Thus, they suggest that amiloride inhibits a sodium channel similar to the apical epithelial sodium channel in the distal nephron. The authors conclude that sodium channels are induced by genomic effects of aldosterone, which result in sodium influx and cell depolarization, creating an electrochemical gradient that leads to chloride and water accumulation and cell swelling. Amiloride, by blocking the sodium channels, hyperpolarizes the cell, leading to chloride efflux followed by efflux of water and cell shrinkage. Whether this interpretation is correct remains to be proven. The authors propose that endothelial cell swelling followed by sodium influx also leads to activation of the sodium/potassium ATPase and potassium influx. They suggest that, considering the huge surface of endothelium, aldosterone may reduce serum concentrations of potassium not only by its renal action but also mediated by inducing potassium entry into endothelial cells as a result of sodium/potassium ATPase activation. Furthermore, amiloride could have opposite effects on the hypokalemia of patients with hyperaldosteronism by leading to rapid potassium shifts from inside swollen endothelial cells. These conclusions remain to be supported by further appropriate animal or clinical experimentation. However, this study adds to the increasing literature that shows that aldosterone exerts important physiologically and/or pathophysiologically relevant effects on the cardiovascular system and on different organs, including the brain, in contrast to the notion that mineralocorticoids are only involved in body electrolyte and water homeostasis mediated by the kidney, which has been accepted for more than half a century.\(^2\)

These same authors also demonstrated by applying atomic force microscopy to endothelial cells that aldosterone rapidly (<10 minutes) induced an increase of the cell nucleus that could reach 15% to 28% of total cell volume and disappeared within 30 minutes.\(^3\) Additionally, they showed that 2 minutes after aldosterone injection into Xenopus laevis oocytes intracellular receptors bound to nuclear pores on the nuclear membrane, which then translocated into the nucleus. Fifteen minutes later macromolecules that resemble ribonucleoproteins and which could carry the aldosterone-induced mRNA to ribosomes were visualized in the central channels of the nuclear pores. They postulated that aldosterone-induced nuclear swelling was a rapid genomic effect as receptors translocated from the cytoplasm into the nucleus and gene transcription followed, with the return of normal nuclear volume when mRNA was exported into the cytoplasm. The authors concluded that responses to aldosterone could no longer be divided into acute nongenomic (<10 minutes) and sustained genomic (>10 minutes) effects, because rapid genomic effects could be demonstrated.\(^3\) They further hypothesized that this phenomenon that resulted in swelling of endothelial cells as described in the current study\(^1\) could affect resistance to blood flow in small arteries.

Aldosterone has been shown to be produced in the heart\(^4,5\) and blood vessels,\(^6,7\) although it is still not established whether the concentrations achieved are high enough to exert local effects.\(^8\) Perhaps more importantly, cardiac and vascular mineralocorticoid receptors have also been demonstrated.\(^9\) Aldosterone has been implicated in the induction of fibrosis in heart, blood vessels, and the kidney, particularly in the presence of high salt.\(^10–13\) In addition, actions that are usually attributed to direct effects of angiotensin II, such as vascular remodeling, endothelial dysfunction via increased oxidative stress, and inflammation of the vascular wall and heart, may in fact be mediated at least in part by aldosterone.\(^14\) An inflammatory cardiovascular and renal response to mineralocorticoids and particularly to aldosterone has been clearly established\(^15–18\) and may occur more easily in the presence of high salt, which seems to sensitize the cardiovascular system to nefarious effects of aldosterone. Inflammatory responses have increasingly been associated with the mechanisms involved in the pathophysiology of cardiovascular disease.\(^19\)

The vascular and cardiac inflammatory response includes upregulation of inflammatory mediators such as NFκB and AP-1, adhesion molecules such as vascular cell adhesion molecule-1 and intracellular adhesion molecule-1, and endothelin-1.\(^20\) It would be of interest to determine if these mechanisms are activated by endothelial cell swelling. The phenomena revealed by Oberleithner et al\(^1\) could then also be

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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implicated not only in regulation of body water and electrolytes, but also in some of the newer pathophysiological effects attributed to aldosterone that participate in cardiovascular disease.

The knowledge that aldosterone may act on the endothelium is not new. It has been suggested that aldosterone may act on endothelial cells to impair endothelial function, which could occur in response to stimulation of oxidant stress by aldosterone.\(^{17,21,22}\) Recently, and in contrast to previous studies, other investigators have demonstrated that rather than a deleterious effect in response to aldosterone, a beneficial action can be observed on endothelial function via phosphatidylinositol 3-kinase-dependent activation of nitric oxide synthase.\(^{23}\) Mineralocorticoids including aldosterone stimulate the production of endothelin-1 in the kidney, vasculature, and heart.\(^{11,12,20,24–27}\) How these effects interplay in the vasculature and the heart to result in the actions of aldosterone during normal body homeostasis and in pathological conditions such as essential hypertension or heart failure is unclear.

A role of aldosterone in essential hypertension has been suggested for many years,\(^ {28}\) and recent data with the new mineralocorticoid receptor blocker eplerenone\(^ {29,30}\) seems to provide further support to this hypothesis. The realization that hyperaldosteronism may be a relatively frequent mechanism of elevated blood pressure and the search for the more numerous cases of primary aldosteronism among hypertensive patients\(^ {31,32}\) add to the interest in both the cardiovascular effects of mineralocorticoids and the potential for new approaches to therapeutic intervention in hypertension. In heart failure, blockade of mineralocorticoid receptors not only improves endothelial function\(^ {21}\) but also reduced events in the Randomized Aldactone Evaluation Study trial\(^ {33}\) and post-myocardial infarction in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study trial.\(^ {34}\) The rather extraordinary saga of aldosterone does not end with these very significant therapeutic findings. The interest in this effector of the renin-angiotensin system may go further. The finding that there are mineralocorticoid receptors in the brain that result in stimulation of the sympathetic nervous system and may induce blood pressure elevation as well as inflammatory responses further complicates and enriches our understanding of the pleiotropic actions of aldosterone.\(^ {35,36}\)

The study by Oberleithner et al\(^ {1}\) may be one of many that will in the near future add to the complexity of our understanding of the multiple targets of aldosterone. Increased mechanistic knowledge of this critical mediator and its many targets will contribute to our ability to act therapeutically to the benefit of patients with cardiovascular disease, including hypertension, ischemic heart disease, stroke, heart failure, and renal disease.

**References**


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