There is increasing evidence for a dependency on aldosterone in the development of hypertension. How aldosterone influences the physiology that determines blood pressure or for that matter promotes the pathophysiology of high blood pressure turns out to be less than straightforward. There is the genomic pathway that begins with the binding of aldosterone to the classical mineralocorticoid receptor (MR) and ends with sodium reabsorption at the distal nephron. But aldosterone can convey nongenomic influences as well, actions that have received less attention, possibly in part because they seem counterintuitive to our genomic view of biology. Adding to the complexity of aldosterone’s actions is the fact that there are also nonepithelial (nondistal nephron) targets of aldosterone, such as the heart, the vasculature, the kidney, and other sites. In this issue of Hypertension, Schmidt et al describe a rapid (thus nongenomic) effect of administered aldosterone to increase resistance in renal vasculature (a nonepithelial target) in healthy human subjects. The findings follow on the heels of a rather large body of work on the genomic actions of aldosterone.

Aldosterone’s nongenomic effects were first recognized more than a decade before an aldosterone-inducible gene was identified in the late 1990s. A nongenomic action characteristically occurs almost immediately, usually within several minutes, before sufficient time has elapsed for gene transcription and synthesis of new protein (the time it takes aldosterone to increase the sodium current, a genomic effect, is \( \approx 30 \) minutes). A novel aldosterone receptor for nongenomic signaling has yet to be identified, but it would seem, if indeed a specific receptor exists, that most likely it is membrane associated. A role for the classical MR has not been ruled out although the MR antagonist, spironolactone, is not usually inhibitory nor is the response lost in MR knockout mice. Nongenomic responses elicited by aldosterone are accompanied by activation of early signal transduction pathways with increases in intracellular calcium, inositol triphosphate, diacylglycerol, and cAMP together with activation of protein kinase C. Most previous nongenomic studies of aldosterone were carried out in vitro or ex vivo, thus limiting the chance for observing potential interactions with other systems. Nongenomic and genomic actions of aldosterone might, for example, importantly interact as was suggested by the in vivo study of Schmidt et al.

They found that the effect of aldosterone on renal vasculature occurred only when endothelial NO synthase (eNOS) was inhibited by simultaneously treating with \( N^G \) monomethyl-L-arginine (L-NMMA); inhibition of eNOS appeared to unmask a nongenomic effect of aldosterone. Although one could argue that this necessary manipulation made conditions too pharmacological, it can just as easily be viewed as a replication of the endothelial dysfunction that is associated with increased risk for cardiovascular disease, as might occur, for example, in patients with the metabolic syndrome. Indeed, the requisite for eNOS inhibition suggests that certain nongenomic vascular effects of aldosterone become manifest only when there is a loss of endothelial integrity. This was nicely demonstrated in earlier studies carried out by Arima et al using isolated renal arterioles.

The interjection of NO into the equation enables the development of a working model wherein genomic and nongenomic influences of aldosterone become integrally dependent. This concept is based on evidence that aldosterone reduces the bioavailability of NO by a genomic-mediated inhibition of eNOS, a conclusion reached from clinical studies where giving spironolactone for 3 months to patients with primary aldosteronism and high aldosterone levels improved endothelial function (there was a more than 2-fold greater flow-mediated dilation of the brachial artery after treating with spironolactone). Had it been possible in the study by Schmidt et al to administer a high dose of aldosterone over a longer period of time or had they included subjects with known endothelial dysfunction, they might have avoided the requisite for the eNOS inhibitor. In a previous study using a dog model of obesity-induced hypertension, both blood pressure and renal glomerular hyperfiltration decreased after treating with eplerenone, a selective MR antagonist. This could be an instance where blocking a genomic pathway (aldosterone-induced inhibition of NO release) prevented the nongenomic pathway (aldosterone’s effect on the vasculature) from developing. It should be noted that in the chronic dog model reducing exposure to endogenous levels of aldosterone by using eplerenone reduced the glomerular filtration rate (GFR), whereas the opposite intervention of giving aldosterone together with L-NMMA also resulted in a lowering of GFR. This disparity in how aldosterone affected GFR cannot with certainly be explained. It is likely that the answer lies in the differences in experimental designs, with fluid and electrolyte shifts affecting hemodynamics and resulting in different renal affects from that observed in the...
acute setting only. The dog model of obesity-induced hypertension is an example of how difficult it might be to separate out a nongenomic effect under conditions where there are probably multiple factors, including genomic factors that operate to maintain the steady state.

Estrogen increases NO synthesis and bioavailability leading to vasodilation and possibly contributing to the sexual dimorphism in blood pressure (such as the lower blood pressures in premenopausal women when compared with age-matched men). Estrogen also has well characterized nongenomic effects and indeed there is a recent description of a membrane receptor that is activated by estrogen. Work in the estrogen field has led to new treatment options, namely the synthesis of an estrogen receptor ligand that preferentially activates a nongenomic pathway in bone. Thus, it would seem likely that drug development could lead to inhibitors of nongenomic actions of aldosterone, should the benefit of such an approach be firmly established. There is in fact evidence that eplerenone may posses such nongenomic properties.

In summary, aldosterone may have important nongenomic vascular effects in the kidney that can ultimately influence blood pressure. There may be buffering of the effect by NO when the endothelium is healthy and aldosterone levels are normal. Since aldosterone appears to decrease the bioavailability of NO through a genomic mechanism, the nongenomic mediated vascular response might be preventable with use of currently available MR antagonists. The future may hold promise for development of inhibitors specifically designed to curtail nongenomic influences. The widespread prevalence of endothelial dysfunction would seem to justify a more intensive examination of the vascular effects of aldosterone, studies that should include additional clinical observations.

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