Letters to the Editor

Rapid Nongenomic Effect of Aldosterone on Vasoconstriction

To the Editor:

Schmidt et al.\(^1\) recently reported in *Hypertension* that aldosterone has a rapid nongenomic vasodilatory effect when infused into the human forearm. Schmitt et al.\(^2\) published a counterpoint to this report by referring to two studies showing the opposite. While we have no intention to interfere in the discussion on the complexity of human forearm studies, we wish to call the attention to two independent animal studies published recently in *Hypertension*’s sister journals *Circulation*\(^3\) and *Circulation Research*.\(^4\) Using in vitro techniques (rat aortic rings and rabbit renal afferent arterioles) it was shown that aldosterone decreases vascular reactivity to phenylephrine and to depolarization. This novel effect was seen already at subpicomolar concentrations of aldosterone, and it was mediated by the mineralocorticoid receptor. Furthermore, the effect of aldosterone was seen within 5 minutes and was not blocked by inhibition of gene transcription, allowing the conclusion that the effect is nongenomic. As to the effector mechanism, both studies concluded that the effect of aldosterone involved phosphatidylinositol 3-kinase-dependent nitric oxide synthase activation and production of nitric oxide. Although these two studies did not report any effect of aldosterone on basal tone of the vessels, Arima et al.\(^5\) recently observed that aldosterone increased basal tone in microperfused afferent arterioles by a mechanism dependent on phospholipase C and calcium mobilization in the smooth muscle cells.

Taken together, the studies support the contention of Schmidt et al.\(^1\) that the effects of aldosterone on vascular function are complex and are likely to depend on a balance between effects on endothelium and smooth muscle, and, in addition, between nongenomic and genomic effects.

Torben R. Uhrenholt
Boye L. Jensen
Ole Skott

Physiology and Pharmacology
University of Southern Denmark
Odense, Denmark

Response: Rapid Nongenomic Effects of Aldosterone on Human Forearm Vasculature

In their comment on our recent report on the rapid nongenomic effects of aldosterone Uhrenholt et al cite three even more recent articles that support our data.

We agree that the results from these in vitro studies strengthen our conclusion that rapid nongenomic effects to the human vasculature exist and are of a complex nature. The comparable data obtained from different experimental models (human forearm,\(^1\) rat aortic rings,\(^2\) rabbit afferent arterioles\(^3\)) support our data derived from the human forearm strongly suggesting that they are not an artifact.\(^4\)

Based on the current knowledge we propose a model for vascular aldosterone effects that is similar to a recently published model for steroid effects in general.\(^5\) Aldosterone affects both endothelial cells (EC) and vascular smooth muscle cells (VSMCs). In EC rapid nongenomic effects cause an increased activity of NO synthase by a phosphatidylinositol 3-kinase-dependent mineralocorticoid receptor (MR) dependent mechanism and, which is controversial, by a MR independent mechanism involving phospholipase C and intracellular calcium. This in turn causes an increased bioavailability of NO and a tendency to vasodilation. In VSMCs aldosterone also causes an increase in intracellular calcium by an MR-independent mechanism using the inositol 1,4,5-triphosphate and diacylglycerine-protein kinase C pathway. This results in a tendency to vasoconstriction. Besides the studies cited by Uhrenholt et al another very recent study supports this view. Arima et al show that endothelium derived NO decreases the vasoconstrictor response to aldosterone in rabbit preglomerular afferent arterioles. Disrupting the endothelium as well as blockade of endothelial NO synthase augmented aldosterone induced vasoconstriction in this study.\(^6\)

In conclusion, there is increasing evidence for complex rapid, nongenomic effects to the vasculature that support our results published in an earlier issue of this journal.\(^1\)

Bernhard M.W. Schmidt
Roland E. Schmieder

Department of Medicine IV/Nephrology
University of Erlangen-Nürnberg, Germany

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Torben R. Uhrenholt, Boye L. Jensen and Ole Skøtt

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