The Adrenergic Nervous System Conversing With the Adrenal Cortex
New Implications for Salt-Sensitive Hypertension

J. Howard Pratt

Adrenocorticosterone signals the distal nephron to reabsorb sodium and secrete potassium. The regulation of aldosterone secretion is driven by the need to defend against sodium deficiency or an elevated potassium. With a high-salt diet, the one typically consumed today, the rigorous relationship of aldosterone to sodium balance begins to break down with the result that more aldosterone is produced than is needed, driving the distal nephron, the guardian of overall sodium homeostasis, to a state of overactivity. Why is aldosterone secretion not more contained under conditions of high salt intake? One explanation is that there were no telescopic pressures applied to the renin–angiotensin system to appropriately dampen stimulation of aldosterone secretion: early ancestral survival depended on there being only sufficiently high levels of aldosterone.1

In the current issue of Hypertension, Pojoga et al2 provide evidence for a new mechanism whereby secretion of aldosterone is sustained under conditions of generous salt intake and when, in the interest of avoiding hypertension, a lower secretion rate would be preferred. They report on an intriguing observation that certain haplotypes (more specifically, diplotypes) of the β-2 adrenergic receptor (β2AR) gene associate with low-renin hypertension that seems to be because of higher plasma aldosterone levels. Theoretically, when something other than the usual stimuli (angiotensin II and potassium) are increasing aldosterone secretion, the usual stimuli downregulate their contribution, and there is no net increase in secretion; but, as already noted, this type of counterregulation may be less than complete under conditions of high salt consumption.

In addition to showing that a certain gene variant may better define a subclass of low-renin hypertension (an observation that will require confirmation), the findings of Pojoga et al2 indicate that 2 very dissimilar biologic systems, the sympathetic nervous system and adrenal steroidogenesis, engage in what may be an important and heretofore unappreciated interaction. Several years ago it was demonstrated that β-adrenergic agonists applied directly to adrenocortical cells stimulate aldosterone secretion (similar findings were made by Pojoga et al2).3,4 Although little is known about how the adrenergic influences reach the adrenal cortex, the outer capsule and the adjoining zona glomerulosa, the site of aldosterone synthesis, are richly innervated with adrenergic fibers and, thus, it could be here that the 2 systems meet.

Alternatively, the adrenal medulla could be the source of catecholamines that affect aldosterone secretion. Chromaffin cells from the medulla have been shown to project through the cortex (“medullary rays”) and terminate in the zona glomerulosa (Figure).5–7 The proportion of epinephrine to norepinephrine in rat adrenal capsule (consisting primarily of zona glomerulosa) has been shown to be similar to that in adrenal medulla with an epinephrine:norepinephrine ratio of ≈5:1,4 further supporting the idea that catecholamines from deep within the adrenal could signal secretion of aldosterone. Aldosterone secretion is highly sensitive to increases in potassium, and one wonders if a transcellular flux of potassium might be the stimulus.

Although evidence is presented that the adrenergic nervous system can affect aldosterone secretion and blood pressure through variations in the β2AR gene, there may be other instances where the 2 ordinarily independent systems converge to increase blood pressure. If one can be allowed to freely speculate, Calhoun and colleagues6,9 have now shown that many patients with sleep apnea meet the criteria for also having primary aldosteronism: could it be “secondary” to intermittent hypoxia driving the sympathetic nervous system to produce more aldosterone? Speculating even further, could it be that the adrenergic nervous system through its anatomic connections to the zona glomerulosa serves as a mediator of the adrenal hyperplasia in the most common form of primary aldosteronism? Although one’s clinical intuition would seem to dictate otherwise, is it possible that a β2AR antagonist, such as a nonselective β-blocker like propranolol, reduces aldosterone secretion? This is probably too farfetched to be compelling. But clearly the article by Pojoga et al2 should at the least cause us to rethink mechanisms for hypertension, including options for treatment.

Source of Funding
Support was provided by National Institutes of Health grant RO1-HL-3579 and by the VA Medical Center. The author has received a National Institutes of Health grant of more than $10 000.

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

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(Hypertension. 2006;48:820-821.)

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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000244561.84382.df
Disclosure

None.

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Hypertension. 2006;48:820-821; originally published online October 2, 2006;
doi: 10.1161/01.HYP.0000244561.84382.df

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/48/5/820

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