New Twist to the Role of the Renin-Angiotensin System in Heart Failure

Aldosterone Upregulates Renin-Angiotensin System Components in the Brain

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The renin-angiotensin system has been shown to be upregulated in peripheral tissues, particularly the vasculature, in a number of different cardiovascular conditions. As well, many actions on the vasculature usually attributed to direct effects of angiotensin II (Ang II) are now known to be mediated at least in part by aldosterone.1,2 In the present issue, Yu et al3 demonstrate that components of the renin-angiotensin system (RAS) are upregulated in the brain in a model of ischemic heart failure in rats. They demonstrate that aldosterone is elevated in heart failure in the brain proportionately to the increase in the circulation. This increase results in mineralocorticoid receptor–mediated stimulation of hypothalamic angiotensin I-converting enzyme (ACE) and angiotensin type 1 (AT1) receptor mRNA and protein, enhanced reduced nicotinamide-adenine dinucleotide phosphate oxidase activity, and reactive oxygen species in the paraventricular nucleus. Activation of the renin-angiotensin system and its mediators leads to increased neuronal activity and sympathetic drive and elevated circulating levels of plasma norepinephrine. All of these effects were blocked in this model by intracerebroventricular administration of a mineralocorticoid receptor antagonist. They suggest that, whereas penetration of aldosterone into the brain correlates with plasma levels but may be variable for ACE inhibitors, AT1, and mineralocorticoid receptor blockers, adequate inhibition of these central effects with these RAS blockers may not be achieved without inducing important adverse effects. Thus, inhibition of aldosterone synthesis or release may be a better approach to reduce these actions of aldosterone on the brain that participate in the pathophysiology of heart failure.

Although Ang II is now well recognized to have direct tissue effects that result in vasoconstriction, growth, inflammation, and progression of atherosclerosis through its vascular effects and sodium and water retention by action on the kidney, all of which contribute to different forms of cardiovascular disease, including hypertension, coronary artery disease, and heart failure, it is only in the past few years that it has become increasingly apparent that aldosterone also has many direct actions on the vasculature.3 In addition and apart from its classical action on the kidney to retain salt and water, aldosterone, which is of course secreted in response to stimulation of the adrenal glomerulosa by Ang II, contributes to either induce or accentuate some of the effects of Ang II.1,2 Aldosterone mediates, in part, some Ang II actions, because, like Ang II, it also stimulates mitogen activated protein kinases, inflammatory mediators, and the generation of reactive oxygen species and, thus, enhances actions of Ang II by cross-talk of the AT1 and mineralocorticoid receptor and/or their signaling pathways.7,8 However, exact mechanisms for these interactions remains unclear. Interestingly, some studies have also shown that the mineralocorticoid receptor may be activated by AngII, although this occurs probably indirectly.9 The cross-talk between mineralocorticoid and AT1 receptors could occur in part in lipid rafts, because the scaffold proteins common to signaling by both receptors result in assembly of a shared pathway leading to activation of mitogen-activated protein kinases and enhanced response to simultaneous stimulation by Ang II and aldosterone.

One of the most interesting aspects of the article by Yu et al10 is perhaps the finding that aldosterone upregulates ACE and AT1 receptors in the brain. Upregulation of the angiotensin receptor in peripheral resistance arteries by mineralocorticoids was demonstrated by us a quarter of a century ago first in the vasculature of the deoxycorticosterone acetate-salt hypertensive rat10 or rats simply infused with deoxycorticosterone acetate,13 then in rats infused with aldosterone and by the effect of aldosterone in vitro on rat vascular smooth muscle cells.12 These studies were extended several years later by Ullian et al,13,14 who showed that signaling of angiotensin receptors was enhanced by aldosterone. Upregulation of ACE by mineralocorticoids in cardiomyocytes was also shown some time ago.15 Thus, in the brain, inappropriate elevated concentrations of aldosterone will, like in the periphery, induce upregulation of ACE and angiotensin receptors, which leads to a vicious circle that, by increasing the concentration and action of AngII, accentuates the pathophysiological effects and tissue damage that the renin-angiotensin system may induce both locally in the brain and systemically.

The careful study of Yu et al3 demonstrates to us once more the complex and ubiquitous actions of the renin-angiotensin-aldosterone system, its nimble nature and ability to
adapt to the environment, and its capacity to interact with many other cascades and systems, including steps within the same renin-angiotensin-aldosterone system. These are the reasons for its important contribution to homeostasis and ability to participate in the modulation of hemodynamic functions and regulation of vital functions, including the maintenance of blood pressure. As well, its many sites of action provide new opportunities for intervention in important disease conditions that contribute in a large measure to the morbidity and mortality of the population, including heart failure, as pointed out by Yu et al. Indeed, the point is made that these actions of aldosterone may best be controlled by reducing the concentrations of aldosterone through inhibition of aldosterone synthase in the adrenal cortex rather than counting on the variable penetration into the brain of agents that may block the central effects of Ang II or aldosterone. Whether such interventions will indeed improve central actions of aldosterone that contribute to pathophysiology in heart failure or other cardiovascular conditions remains to be established.

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