Sympathetic Hyperactivity in Hypertensive Chronic Kidney Disease Patients Is Reduced During Standard Treatment

To the Editor:

Sympathetic activation is of crucial importance for both the blood pressure increase and the high morbidity and mortality in end-stage renal disease.1 The mechanisms responsible for increased sympathetic outflow remain to be elucidated. In their latest of a series of informative studies in patients with chronic kidney disease (CKD), Neumann et al2 report a reduction in muscle sympathetic nerve activity by decreasing the activity of the renin–angiotensin–system with angiotensin-converting enzyme inhibitors or angiotensin II type 1-receptor blockers, suggesting either a cause and effect relationship between the 2 or, alternatively, a common origin, such as kidney ischemia.

Although experimentally it is well established that angiotensin II facilitates norepinephrine release, its role in sympathetic activation in humans is less well documented. In another model of high sympathetic tone, namely, essential hypertension, we have used 2 different approaches to address these issues. First, in a randomized, placebo-controlled crossover study, we prospectively evaluated whether angiotensin II type 1-receptor blockers had identifiable antiadrenergic properties, as assessed by changes in muscle sympathetic nerve activity and whole body norepinephrine spillover.3 Despite comparable muscle sympathetic nerve activity (35 ± 12 bursts per minute) in hypertensive patients on placebo compared with the CKD patients studied by Neumann et al (33 ± 11 bursts per minute),2 angiotensin II type 1-receptor blockers had no effect on either of the 2 parameters measured, indicating that the angiotensin II type 1-receptor blockers did not materially inhibit central sympathetic outflow or act presynaptically to reduce norepinephrine release at existing rates of nerve firing. In a second investigation, using a more direct approach,4 we combined measurements of systemic and cardiac sympathetic activity with simultaneous determination of arterial and coronary sinus plasma concentrations of angiotensin I and II. Again, our study did not provide any support for facilitation of cardiac norepinephrine release by angiotensin II in hypertensive subjects, despite markedly elevated systemic and cardiac spillover of norepinephrine.

Taken together, these studies clearly demonstrate sympathetic activation both in essential hypertension and CKD, but perhaps with a different role for central and/or peripheral angiotensin II neuromodulation. The observation that eprosartan reduced heart rate in CKD patients,2 together with experimental data from the pithed rat model revealing that eprosartan was the most potent inhibitor of facilitation of sympathetic neurotransmission,5 gives ground to the assumption that these mechanisms may indeed be relevant in humans with CKD. To unravel the underlying mechanisms, it will be necessary to study regional sympathetic activation using norepinephrine kinetics. The intriguing hypothesis that kidney ischemia may be the cause of sympathetic augmentation in CKD and perhaps other conditions known to impact on renal blood flow, such as essential hypertension and congestive heart failure, warrants further investigation.

Disclosures

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