To the Editor:

Several articles have appeared recently on the role of tissue prorenin in the pathogenesis of cardiovascular and renal damage in experimental models of hypertension and diabetes mellitus1-3 including the study by Ichihara et al,3 published in Hypertension and accompanied by an editorial comment.4 Thus, in rats with streptozotocin-induced diabetes, blockade of nonproteolytic activation of prorenin by the “handle peptide” prevented development of nephropathy and associated proteinuria.1 Similarly, in diabetic mice with angiotensin II type 1a receptor deficiency, blockade of the prorenin receptor prevented development of glomerulosclerosis by impeding activation of mitogen-activated protein kinase.2 Finally, in the stroke-prone spontaneously hypertensive rat, administration of a prorenin inhibitor for 8 weeks significantly attenuated development and progression of cardiac fibrosis without affecting elements of circulating renin–angiotensin system or arterial pressure.5

We have also examined the cardiovascular effects of prorenin blockade in the spontaneously hypertensive rat (SHR), an excellent experimental model of essential hypertension. To this end, male, 20-week-old, SHRs were divided into 2 groups and implanted subcutaneously with osmotic minipumps (Alzet, model 2ML4 for 28 days) containing either the handle peptide (PRAM1 >99% pure; Pneumosite, LLC) that inhibits nonenzymatic activation of prorenin in a dose of 0.1 mg/kg per day or an inert vehicle (distilled water). Systemic and regional (including coronary) hemodynamics (radiomicrospheres), left ventricular function (using catheter-tip transducer), cardiovascular mass indices, and degree of cardiac fibrosis (collagen volume fraction) were examined during the fourth week of treatment. Similar to the findings of Ichihara et al,3 we found that blockade of nonenzymatic prorenin activation did not affect systemic hemodynamics but consistently reduced left ventricular mass (2.81±0.04 mg/g versus 2.59±0.03 mg/g in controls versus treatment, respectively; P<0.05). However, we did not demonstrate any effect of prorenin blockade on myocardial collagen content, left ventricular function, and coronary and renal hemodynamics. In contrast, we have shown previously that 3-week treatment of young adult SHRs with angiotensin II type 1 receptor antagonists5 reduced left ventricular mass and fibrosis and improved coronary hemodynamics. These findings, together with our aforementioned data, suggest that a limited exposure (eg, 4 weeks) to prorenin inhibition did not reverse cardiovascular damage in SHR. Because blockade of tissue prorenin release in earlier studies by others with the same blocking agent for a similar time period inhibited damage in the diabetic kidney, unlike the SHR heart in the present study, it is possible that the degree of inhibition or the kinetics of inhibition by a given dose of this prorenin inhibitor may vary among peripheral organ systems.1 Alternatively, nonenzymatic activation of cardiac or renal prorenin may participate in mediating cardiac and renal damage in more acute and more severe forms of experimentally induced disease states, including hypertension aggravated by salt excess or streptozotocin-induced diabetes. Because cardiac and renal damage progress slower in naturally occurring forms of hypertension, such as in the SHR, prorenin inhibition may have limited influence on end-organ damage; however, such a conclusion requires further investigation.

Disclosures

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