Calcitonin Gene-Related Peptide and Sympathetic Nervous System in Hypertension-Induced Renal Damage

To the Editor:

We read with great interest the recent article by Bowers et al. dealing with the role of calcitonin gene-related peptide (CGRP) in hypertension-induced renal damage. The results of their study demonstrated that the deoxycorticosterone (DOC)-salt hypertensive α-CGRP knockout (KO) mice displayed markedly enhanced and progressive renal damage and expression of inflammatory markers in the immunohistochemical investigation. In addition, they indicated that the DOC-salt hypertensive α-CGRP KO mice exhibited elevated urinary biomarkers of oxidative stress and a marked reduction in kidney function compared with the DOC-salt wild-type mice. The authors proposed that sensory nerves, via α-CGRP, might be renoprotective against hypertension-induced damage.

Several studies have reported that enhanced activity of sympathetic nervous system might actively participate in the pathogenesis of renal damage in hypertension. In a study we presented previously, the change in norepinephrine (NE) release induced by α-CGRP was investigated in rat central nervous system. In an in vitro study, we showed that α-CGRP inhibited the stimulation-evoked NE release in a dose-dependent manner. It was also demonstrated that a dihydropyridine-sensitive calcium (Ca) channel agonist Bay K 8644 significantly reversed the inhibitory effect of α-CGRP on NE release, indicating that α-CGRP might partially interact with dihydropyridine-sensitive Ca channels and modulate intracellular Ca mobilization. Furthermore, we showed that the inhibitory action of α-CGRP on NE release was significantly attenuated in spontaneously hypertensive rats compared with normotensive rats. In the peripheral tissues, Ohhashi and Jacobowitz observed that α-CGRP reduced the electrical stimulation–induced contraction of rat vas deferens, suggesting that α-CGRP might inhibit NE release during adrenergic nerve stimulation. It can be speculated that impaired modulation of NE release in the absence of α-CGRP might cause sympathetic hyperactivity and could contribute, at least in part, to the pathogenesis of renal damage. Therefore, we would like to know whether changes in sympathetic nervous activity might be correlated with the magnitude of renal damage in the DOC-salt hypertensive α-CGRP KO mice in the present study of Bowers et al. Further studies should be performed to assess more thoroughly the interactions between CGRP-containing sensory nerves and sympathetic nervous system and their role in hypertension-induced renal damage.

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Response

In response to Dr Tsuda’s letter to the editor with regard to our article, “Role of Calcitonin Gene-Related Peptide in Hypertension-Induced Renal Damage,” we would like to express our appreciation for Tsuda’s comments. These comments were focused on the possible involvement of the sympathetic nervous system in the renal damage observed in the DOC-salt hypertension–induced α-calcitonin gene-related peptide (α-CGRP) knockout (KO) mouse model. Specifically, Tsuda’s question was whether changes in the activity of the sympathetic nervous system might be correlated with the magnitude of renal damage in the DOC-salt hypertensive α-CGRP KO mice compared with their wild-type (WT) counterparts used in our study. Tsuda correctly describes several lines of evidence demonstrating that α-CGRP can inhibit norepinephrine release in the central nervous system and peripheral tissues and postulated that the lack of α-CGRP could produce sympathetic hyperactivity, thereby contributing to the observed renal damage described in our article. In this report, we stated that there are 3 possible mechanisms that may underlie our observations. The first is the higher absolute mean arterial blood pressures in the DOC-salt hypertensive α-CGRP KO mice compared with the hypertensive WT animals. The second is a direct effect of the lack of α-CGRP, and the third is that permanent deletion of the α-CGRP gene could significantly alter the activities of other neurohumoral systems that regulate blood pressure and contribute to hypertension-induced end organ damage, such as the sympathetic nervous system and the renin-angiotensin system. We did, in fact, specifically site studies reporting that in the absence of hypertension producing protocols, α-CGRP KO mice displayed significant increases in the activities of the sympathetic nervous system and the renin-angiotensin system. Indeed, equal weight was given to each of the 3 possible mechanisms because the experimental design of our study did not allow us to differentiate between them.

The first priority of our laboratory is to investigate the most crucial question arising from this study, which is the role of the blood pressure differential between the DOC-salt hypertensive α-CGRP and WT mice on the severity of the renal damage. This was done by decreasing the blood pressure (as measured by telemetric recording) in the KO mice by the administration of hydralazine in the drinking water. The results from our initial studies will be presented at the American Heart Association 59th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research in September. Once this series of experiments is completed, we will assess the participation of the sympathetic nervous system (and the renin-angiotensin-aldosterone system) in this model, as requested by Dr Tsuda.

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