Angiotensin II-Induced Regulation of Iron-Mobilization Gene Expression and Deposition of Iron in the Target Organs in vivo

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Activation of renin angiotensin system (RAS) is now considered to be a major underlying cause of target organ damage in the condition of hypertension, diabetes, and heart failure. The mechanisms by which RAS evokes end-organ damage may include the overproduction of superoxide, which is mediated by the activation of membrane-bound NADPH oxidase system, and by the subsequent enhancement of oxidative stress. Excessive iron may potently further increase the toxicity of such reactive oxygen species by promoting the generation of lipid peroxidation, presumably, in part, via catalyzing the generation of hydroxyl radicals. We sought to investigate the accumulation of iron in various organs in rats that were receiving continuous administration of angiotensin II. It was found that 7-day angiotensin II administration caused deposition of iron in the proximal tubules of the kidney, granulation regions of the heart, adventitial cells of the aorta, and interstitial macrophages in the liver. Angiotensin II administration was also found to increase the circulating levels of 8-epi-prostaglandin $F_{2\alpha}$, which was suppressed by the chelation of iron. Iron chelation ameliorated functional damage of kidney and aorta in the rats given angiotensin II, suggesting that modulation of iron homeostasis may play a role in the enhancement of oxidative stress and oxidant-induced organ damage induced by angiotensin II. Then we examined the regulation of expression of several iron mobilization-related genes, such as DMT-1, ferroportin, and hepcidin, was examined, and found that expression of some these genes were regulated in mRNA level by angiotensin II administration.