Editorial Comment

Inflammation and Salt Sensitivity in the Early State of Hypertension

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(*Hypertens Res* 2007; 30: 105–107)

***Key Words*: prehypertension, metabolic syndrome, renin-angiotensin aldosterone system, monocyte chemotactic protein-1**

Both genetic and environmental factors play a pivotal role in the pathogenesis of hypertension. A cross or congenic model using genetically hypertensive rats is a powerful tool to restrict the quantitative trait loci (QTLs) responsible for high blood pressure (BP) into small intervals. The Dahl salt-sensitive (SS) rat closely mimics human salt-sensitive hypertension and is appropriate for examining the underlying genetic mechanism of the organ damage that occurs with excess salt intake. Previous studies have revealed several major QTLs responsible for high BP in SS rats. In addition to QTL mapping, the exhaustive expression profiling can be used to elucidate the candidate gene in the QTL. In this issue of *Hypertension Research*, Yasui *et al*. (*1*) found that the monocyte chemotactic protein-1 (MCP-1) gene (chemokine, CC motif, ligand 2: *CCL2*) in chromosome 10 is a new candidate for salt-sensitive hypertension using QTL analysis and expression profiling.

Salt loading in humans and experimental animals causes progressive increases not only in BP but also in endothelial dysfunction and renal damage. Oxidative stress is the most popular explanation in terms of the underlying mechanism in the organ damage of salt-sensitive hypertension. Reactive oxygen species (ROS) are elevated and antioxidant capacity is decreased in hypertensive subjects, many of whom develop end-stage renal disease (ESRD), and SS rats exhibit increased mesenteric microvascular and renal superoxide production and increased plasma levels of H_2O_2 (*2*). Indeed, tempol decreases renal cortical and medullary superoxide anions ($O_2^{\bullet -}$), urinary protein excretion, the percentage of sclerotic glomeruli, and the kidney weight-to-body weight ratio of SS rats (*3*, *4*). Treatment with *N*-acetylcysteine and vitamins C and E improves renal dysfunction, lessens renal injury, and decreases arterial pressure in SS rats, suggesting the importance of oxidative stress in salt-sensitive hypertension and renal damage (*5*, *6*). Low dose administration of an angiotensin II receptor blocker also normalizes ROS production and endothelium-dependent relaxation in SS rats without affecting their BP (*7*, *8*). These results suggest that an inappropriate augmentation of intrarenal angiotensinogen may contribute to the impaired sodium excretion in the development of hypertension in SS rats. Enhanced intrarenal angiotensinogen mRNA and/or protein levels have been observed in genetic hypertension, including not only SS rats but also spontaneously hypertensive rats (SHR), as well as in kidney diseases such as diabetic nephropathy, immunoglobulin A (IgA) nephropathy, and radiation nephropathy (*9*). Furthermore, several single nucleotide polymorphisms (SNPs) in the angiotensinogen gene have been denoted as genetic predisposing factors for salt-sensitive hypertension in humans (*10*).

In addition to oxidative stress, increased lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1) and MCP-1 have been observed in SS rats and salt-sensitive hypertensive subjects independent of BP (*8*). MCP-1, a member of the small inducible gene family, affects the recruitment of monocytes to sites of injury and infection. An alternative description of MCP-1 is given in the Online Mendelian Inheritance in Man (OMIM #158105) database of the National Center for Biotechnology Information (NCBI), where MCP-1 is referred to as "a modifier of coronary artery disease." The A(−2518)G polymorphism of *CCL2* increases the Lp(a)

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Received December 18, 2006.

level, with the result that subjects with the GG genotype are significantly predisposed to coronary artery disease (*11*). In cardiovascular disease, a major effect of MCP-1 is recruitment of monocytes into the arterial subendothelium, which is the earliest step in atherogenesis. Compared to salt-resistant patients, salt-sensitive hypertensives show age-adjusted increases in p-selectin, e-selectin, and MCP-1, but not e-selectin, after adjustment for BP values (*12*). In addition, there is much evidence that MCP-1 is increased after the enhancement of the renin-angiotensin aldosterone system (RAAS) or the occurrence of an enhancement of systemic hypertension (*13*). However, Yasui's paper suggested the possibility that the expression of *CCL2* is increased prior to hypertension (*1*), and another paper also revealed that renal infiltration of immune cells increased arterial pressure and renal damage, and also decreased glomerular filtration rate (GFR) and renal plasma flow in SS rats (*14*). These results support the hypothesis that tubulointerstitial inflammation, especially when accompanied by microvascular disease, plays a pivotal role in the pathogenesis of salt-sensitive hypertension (*15*). Interestingly, the QTL including *CCL2* on chromosome 10 of SS rat is associated not only with high BP and but also with high uric acid level. The RAAS blockade is the most effective way to prevent diabetes and deterioration of renal function, and thus the patients most indicated for this treatment are subjects with metabolic syndrome who have visceral obesity, insulin resistance, and/or higher levels of uric acid. A recent large clinical trial, the Trial of Preventing Hypertension (TROPHY) study, showed that candesartan treatment of prehypertensive subjects appeared to be well tolerated and reduced the risk of new onset of hypertension (*16*). In addition, insulin at physiologically relevant concentrations exerts an inhibitory effect on MCP-1, suggesting an anti-inflammatory and potential antiatherogenic effect of insulin (*17*).

If the relation between RAAS enhancement and inflammation in the early stage of hypertension could be fully clarified, this would be a major breakthrough that could lead to the development of new targets for the prevention of life-style related diseases. However, many missing pieces must be provided to complete the puzzle. A recent publication showing the function of the gene encoding the kinase WNK4 might be a missing piece to explain the underlying mechanism of salt-sensitive hypertension (*18*). WNK4, a causative gene of pseudohypoaldosteronism (PHA II), is considered to be a molecular switch that regulates the balance between NaCl reabsorption and K^+ secretion by altering the mass and function of the distal convoluted tubules through its effect on the Na-Cl cotransporter, NCC. Future investigations will be needed to examine the effect of WNK4 on RAAS, inflammation and oxidative stress in the early stage of hypertension of genetically hypertensive rats and its correlation with salt sensitivity.

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