NKCC1 as an Epigenetically Regulated Transporter Involved in Blood Pressure Elevation With Age

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The ubiquitous Na+,K+,2Cl− cotransporter (NKCC1) belongs to the superfamily of Cl−-coupled carriers providing electroneutral symport of monovalent ions. In vascular smooth muscle cells (VSMC), high-ceiling diuretics such as furosemide and bumetanide, known to be potent inhibitors of these carriers, decrease the concentration of intracellular chloride ([Cl−]), hyperpolarize the sarcolemma and attenuate Ca2+ influx though voltage-gated channels. These studies disclosed the mechanism underlying the inhibitory action of high-ceiling diuretics on VSMC contractions and allowed researchers to hypothesize that enhanced NKCC1 contributes to hypertension via the elevation of vascular tone. This hypothesis was consistent with positive correlations between NKCC1 activity and blood pressure in F2 hybrids of spontaneously hypertensive (SHR) and normotensive rats, attenuation of blood pressure in mice lacking Nkcc1 and the absence of the inhibitory actions of high-ceiling diuretics on contractions and myogenic tone in resistance arteries isolated from Nkcc1−/− mice (for recent review see ref. 1).

Recently, Lee and coworkers reported that increased Nkcc1 mRNA and protein content in the aorta and heart of SHR is accompanied by hypomethylation of the Nkcc1 promoter. In this issue of the American Journal of Hypertension, the same research team demonstrated that methylation of Nkcc1 promoter in normotensive WKY rats was increased with age whereas in SHR it was remained hypomethylated after development of hypertension. Importantly, both increased Nkcc1 expression and inhibitory action of bumetanide on mesenteric artery contractions triggered by activation of α-adrenergic receptors were increased with age in SHR but not in WKY rats. They also found that at 18 weeks of age the activity of DNA methyltransferase 3B in the aorta of WKY was threefold higher than that of age-matched SHR. Viewed collectively, these data strongly suggest that the maintenance of hypomethylation in Nkcc1 promoter due to the decreased DNA methyltransferase 3B activity underlies age-dependent development of hypertension in SHR via augmented expression of this carrier in VSMC that, in turn, leads to depolarization and contraction of resistance arteries.

It is well-documented that in VSMC NKCC1 is activated by vasoconstrictors and inhibited by cyclic adenosine monophosphate-raising vasodilators. Does this reciprocal regulation of NKCC1 contribute to the augmented vascular resistance and chronic elevation of systemic blood pressure? Side-by-side with SHR, NKCC1 is also increased in VSMC from rats with secondary doxycorticosterone acetate-salt hypertension. Do “hypertensive environments,” such as augmented salt consumption and mineralocorticoid secretion, lead to the activation of this carrier via epigenetic mechanisms disclosed by Cho and coworkers? Epigenetically activated NKCC1 may be considered as a potential pharmacological target in hypertension. It should be noted, however, that in rodents side-by-side with elevation of systemic blood pressure via augmented contractions triggered by modest depolarization and activation of α-adrenergic and purinergic receptors, NKCC1 increases the myogenic tone of renal afferent arterioles and mesenteric arteries. Does increased NKCC1 protect the kidney, brain, heart, and other encapsulated organs against the damage caused by high systemic blood pressure via elevation of myogenic tone in the local microcirculation? This comment should be considered in the search for new pharmacological tools targeting this carrier.

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