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Special feature: cardiovascular-kidney interactions in health and disease

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THIS ISSUE CONTAINS 11 refereed manuscripts that describe work presented at the eighth Cardiovascular-Kidney Interactions in Health and Disease Meeting at Amelia Island Plantation, FL, on May 27–30, 2005. The three-day meeting featured original contributions on a broad range of topics including redox regulation and microvascular function, genetic and cellular regulation of vascular growth and function, and growing points in hypertension and cardiovascular disease. A central theme of many presentations was the emerging evidence for oxidative stress as a proximate step in the processes that lead to hypertension and cardiovascular-kidney damage. This topic has been reviewed recently (12). Twenty-four senior investigators participated. The meeting was funded by the Cardiovascular-Kidney Institute of Georgetown University (Washington, DC), the George E. Schreiner Chair of Nephrology at Georgetown University, and by generous educational grants from Pfizer (New York, NY), CV Therapeutics (Palo Alto, CA), Merck (Whitehouse Station, NJ), Amgen (Thousand Oaks, CA) and Novartis Pharmaceuticals (East Hanover, NJ).

Although reactive oxygen species (ROS) have been implicated in the regulation of renal sodium transport (Na+) and in the pathogenesis of salt-sensitive hypertension, the mechanisms whereby superoxide (O2−) regulates renal tubule transport remain unclear. O2− increases sodium chloride (NaCl) absorption in the thick ascending limb of Henle’s loop (THAL) in the absence of nitric oxide (NO), suggesting a direct effect on Na+ transport. The study of Juncos et al. (3) tested the hypothesis that the stimulatory effect of O2− on net NaCl absorption is due to increased Na+/H+ exchange. They examined the effect of exogenous O2− on total, apical and basolateral Na+/H+ exchange in isolated perfused THALs. Exogenous O2− was shown to stimulate apical Na+/H+ exchange and inhibit basolateral Na+/H+ exchange. This predicts that O2− enhances sodium bicarbonate (NaHCO3) absorption. Thus regulation of THAL Na/HCO3 absorption by O2− may underlie the pathogenesis of several forms of hypertension and acid/base disturbances.

Magnesium (Mg2+) is concentrated within cells where it regulates many enzymes. It can antagonize the effects of calcium and thereby may determine vascular smooth muscle cell (VSMC) contraction/dilation. Depletion of cellular Mg2+ increases vascular tone and reactivity, generates oxidative stress, and triggers vascular remodeling and hypertension. Recent findings have shown that the transient receptor potential melastins (TRPMs) 6 and 7 regulate Mg2+ cellular influx. Therefore, the study by Touyz et al. (11) on the role of these proteins in ANG II-dependent Mg2+ uptake by VSMCs is timely. TRPM7 expression is increased by ANG II in VSMCs from Wistar-Kyoto but not in spontaneously hypertensive rats (SHR), which also failed to increase intracellular Mg2+ with ANG II. These studies suggest that TRPM7 is a critical mediator of cellular Mg2+ homeostasis and its response to ANG II, which is modified in hypertension.

Recent studies have characterized the interaction between dopamine and ROS. Activation of dopamine1 (D1)-like receptors (D1 and/or D5) induces an antioxidant response. Yang et al. (13) tested the hypothesis that stimulation of the D5 receptor inhibits NADPH oxidase activity and the production of ROS. They report that NADPH oxidase protein expression (gp91phox, p47phox, and Nox 4) and activity in kidney and brain, as well as plasma thiobarbituric acid-reactive substances (TBARs) were increased in D5 receptor-deficient (D5−/−) mice and that inhibition of NADPH oxidase with apocynin normalizes BP, renal NADPH oxidase activity, and plasma TBARs in these mice. They also report that stimulation of the D5 receptor in HEK-293 cells, which heterologously express human D5 receptor, decreases NADPH oxidase activity, expression of one of its subunits (gp91phox), and ROS production. Finally, they show that these effects of the D5 receptor on NADPH oxidase activity are independent of cAMP/PKA but are partially dependent on phospholipase D2.

There is growing evidence of an important interaction between endothelin (ET) and sympathetic nerve activity (SNA). Recent studies by Dai et al. (1) suggest that ET may increase SNA in deoxycorticosterone acetate-salt hypertension through an action at endothelin-type BCETB receptors on cell bodies of postganglionic sympathetic neurons. To investigate the physiological relevance of these findings, Lau and colleagues (4) determined the role of ETB receptors in the in vivo increase in O2− in sympathetic ganglia. ETB receptor activation was shown to increase dihydroethidium oxidative fluorescence. They further tested whether increases in O2− could be attributed to elevated BP by responses to a pressor dose of phenylephrine. Their findings demonstrate in vivo that ETB receptor activation increases O2− in sympathetic ganglia due to both its pressor effects and to direct stimulation of ETB receptors. Thus O2− in sympathetic ganglia may participate in ET-dependent hypertension by facilitating nicotinic neurotransmission.

20-Hydroxyeicosatetraenoic acid (HETE) synthesis may mediate cerebral vasoconstriction after subarachnoid hemorrhage (SAH), although the factors released by clotting blood that release 20-HETE and the mechanisms by which 20-HETE interacts with the other constricting factors to reduce cerebral
glomerular capillary pressure (Pac) during acute pressor doses, they also investigated NO deficiency secondary to CKD in this rat strain, they also investigated NTOS inhibition causes hypertension and progressive CKD. Erdely and colleagues investigated the response to chronic, high-dose NOS inhibition in the WF. Because of the resistance to CKD in this rat strain, they also investigated glomerular capillary pressure (Pac) during acute pressor doses of NOS inhibitors in the normal WF. The novel findings are that WF rats are protected from CKD after NOS inhibition. Indeed, after chronic NOS inhibition, glomerular injury and proteinuria are minimal in WF at low or high doses of 1NAME. Acute systemic NOS inhibition in the WF resulted in a substantial pressor response but a minimal increase in Pac, which is in contrast with the large increase in Pac in Sprague-Dawley rats. Thus long-term maintenance of Pac during chronic NOS inhibition may protect against CKD in WF rats.

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure, and severe endothelial damage. HUS can be a complication of human immunodeficiency virus type 1 (HIV-1) infection in children, where there are additional microangiopathic lesions in renal capillaries and microcystic tubular dilations that contribute to rapid loss of renal function. Fibroblast growth factor-2 (FGF-2) is released by damaged endothelial cells and accumulates in patients with HIV/HUS. Its activity is modulated by a binding protein (FGF-BP). Therefore, Ray et al. studied the expression and localization of this protein in a mouse model of HIV-1 renal disease. They observed upregulation of FGF-BP associated with the development of the tubular dilation and accumulation of FGF-2. These findings link FGF-BP, perhaps produced by regenerating renal tubular cells, to angiogenic activity in the renal capillaries, which may be important in progression or repair of renal damage in this syndrome.

ANG II plays a key role in vascular remodeling after vascular injury in cardiovascular disease (CVD). The proliferative actions of ANG II are dependent on its type 1 receptor (AT1R). Lee et al. studied the regulation of mRNA synthesis and ANG II receptor expression in proliferating VSMCs. They detected a dissociation between mRNA synthesis and receptor expression, which ascribed to changes in the efficiency of translation of the message and in the RNA-protein complex formed in the cytosol. These new findings demonstrate that AT1R expression during proliferation is regulated posttranscriptionally in part by RNA binding proteins that interact with the specific mRNA.

A second study by Lee et al. investigated the role of these RNA-binding proteins in the expression of AT1R in cultured rat renal medullary interstitial cells. Increasing osmolality reduces ANG II binding to AT1R in these cells. Clearly, this could provide a link between angiotensin action and hydration status. Using this model, the investigators again dissociated AT1R expression from expression of its mRNA and showed that this can be ascribed to an osmotically regulated RNA-protein complex formation.

Vascular shear stress is critical for normal vascular function. An increase in shear releases endothelium-derived relaxing factor/nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Recent studies have indicated that PECAM-1 may transduce shear stress on endothelial cells. Thus the study by Liu et al. that focused on the platelet endothelial cell adhesion molecule 1 (PECAM-1) knockout mouse is of particular interest. They demonstrate that flow-mediated dilation is reduced in the PECAM-1 knockout mouse. This is ascribed, in part, to conversion of NO to peroxynitrite (ONOO−), which reduces dilation from PG12 and EDHF. Clearly, the findings show that PECAM-1 is a major transducer of shear stress in blood vessels.

Although oxidative stress is acknowledged to accompany all the well-characterized models of hypertension and CVD, therapeutic strategies based on vitamin E have been disappointing. Therefore, there is interest in novel approaches using catalytic antioxidants such as the SOD mimetic nitroxide, tempol. The mechanism of acute antihypertensive action of nitroxides in the SHR was studied by Patel et al. They used a family of nitroxides and compared antihypertensive actions in vivo to SOD activity in vitro. The antihypertensive action of 6-membered ring nitroxides correlated closely with the measured SOD activity. This effect occurred within minutes and was quickly reversible. In contrast, SOD had a delayed action. They conclude that nitroxides act as SOD mimetics in this rat model and that the small size of nitroxides compared with SOD provides a more rapid and effective means to lower the BP.

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REFERENCES


