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Altered vascular and renal nitric oxide (NO) system in hypertension

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Hypertension has been related to a diminished activity of NO system. The vasorelaxation in response to endothelium-dependent vasodilators is blunted in patients with hypertension or prehypertension as well as in various animal models of hypertension.
A down-regulation of vascular eNOS has been known in various models of hypertension. The similar magnitude of hypertension between the triply n/i/eNOS null and the singly eNOS null mice suggests that a deficient eNOS activity is mainly responsible for the development of high blood pressure. The expression of eNOS also decreased in the kidney in hypertension, and the reversal of hypertension following unclipping the renal artery was associated with restoration of eNOS expression in two-kidney, one clip (2K1C) hypertension. Each unit of increase in eNOS expression led to a 0.88-fold decrease in the risk of hypertension in autosomal dominant polycystic kidney disease.
The expression of nNOS decreased in the brainstem in spontaneously hypertensive rats (SHR) and Dahl salt-sensitive (DS) hypertensive rats, along with enhanced sympathetic tone. It is likely that NO produced by nNOS prevents the salt-sensitive hypertension, and its down-regulation contributes to the salt-sensitivity in DS rats. The vascular expression of nNOS was also decreased in deoxycorticosterone acetate (DOCA)-salt and 2K1C hypertension. In transgenic rats with inducible angiotensin II (AII)-dependent malignant hypertension, the blood pressure was augmented following the administration of s-methyl-L-thiocitrulline (nNOS inhibitor). On the contrary, the vascular expression of nNOS increased in SHR, which was stimulated by AII. In the kidney, both eNOS and nNOS were upregulated in AII-induced hypertensive rats. The urinary excretion of NO, along with its tissue contents in the kidney, increased in SHR and AII-induced hypertensive rats. The decreased or increased availability of NO derived from eNOS/nNOS may affect the degree of hypertension, either augmenting or ameliorating it.
The expression and activity of iNOS in hypertension is controversial. It was either undetected or apparently expressed in SHR and stroke-prone SHR. The progression of vascular dysfunction was associated with an abnormal expression of iNOS in L-NAME-induced hypertension. An upregulation of iNOS was also noted in essential hypertensive humans, along with an impaired NO-dependent vasodilation. The attenuated expression of iNOS by antihypertensive

therapy may indicate that its upregulation is a consequence, rather than a causative factor, of the high blood pressure.
In the kidney, NO may enhance the urinary excretion of sodium by inhibiting its tubular transport and increasing the glomerular filtration rate, of which blockade may result in positive sodium balance and development of hypertension.
An imbalance between NO and reactive oxygen species (ROS) is a pathognomonic in hypertension. Superoxide generation is increased in hypertension, which may promote the expression of eNOS through transcriptional and post-transcriptional mechanisms. Indeed, an increased expression and activity of eNOS has been noted in hypertension. Superoxides also interact with NO to yield peroxynitrites, reducing the biological half-life and bioavailability of NO. The production of ROS also disturbs the balance between de novo synthesis and oxidation/degradation of BH4. A reduced bioavailability of BH4 causes uncoupling of eNOS and generates more superoxides instead of NO, such as in SHR and DOCA-salt hypertensive rats. The superoxides may also trigger desensitization of vascular sGC, contributing to the hypertension.