Resistance artery remodeling in deoxycorticosterone acetate-salt hypertension is dependent on vascular inflammation: evidence from m-CSF-deficient mice.

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Abstract

Deoxycorticosterone acetate (DOCA)-salt hypertension has an important endothelin-1 (ET-1)-dependent component. ET-1-induced vascular damage may be mediated in part by oxidative stress and vascular inflammation. Homozygous osteopetrotic (Op/Op) mice, deficient in macrophage colony-stimulating factor (m-CSF), exhibit reduced inflammation. We investigated in osteopetrotic (Op/Op) mice the effects of DOCA-salt hypertension on vascular structure, function, and oxidative stress, the latter as manifested by reduced nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase activity. Mice were implanted with DOCA (200 mg/mouse, under 5% isofluorane anesthesia) and given saline for 14 days. Systolic blood pressure (mmHg) was significantly increased (146 +/- 2 and 138 +/- 1; $P < 0.001$ vs. basal 115 +/- 3 and 115 +/- 3, respectively) by DOCA-salt in wild-type (+/+) and heterozygous (Op/+) mice, but not in Op/Op mice (130 +/- 1 vs. basal 125 +/- 3). Norepinephrine contractile response was significantly enhanced, while acetylcholine endothelium-dependent vasodilation was significantly impaired in DOCA-salt-treated +/+ and Op/+ mice compared with control mice. No changes in norepinephrine-induced contraction and acetylcholine-induced relaxation were observed in DOCA-salt Op/Op mice. DOCA-salt +/+ and Op/+ mice had significantly increased mesenteric resistance artery media-to-lumen ratio and media cross-sectional area, neither of which were altered in Op/Op mice. Basal vascular superoxide production and NAD(P)H oxidase activity, vascular cell adhesion molecule-1 expression, and macrophage infiltration were significantly increased only in DOCA-salt +/+ mice. Thus m-CSF-deficient mice developed less endothelial dysfunction, vascular remodeling, and oxidative stress induced by DOCA-salt than +/+ and Op/+ mice, suggesting that inflammation may play a role in DOCA-salt hypertension, a model that results in part from effects of ET-1, which has proinflammatory actions.