Reduced macrophage-dependent inflammation improves endothelin-1-induced vascular injury.

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Abstract

Transgenic mice with endothelium-specific endothelin-1 (ET-1) overexpression exhibit endothelial dysfunction and vascular remodeling, oxidative stress, and inflammation. We previously observed that monocytes/macrophages play a role in angiotensin II, aldosterone, and deoxycorticosterone acetate/salt-induced vascular remodeling, oxidative stress, and inflammation using a model with reduced monocytes/macrophages, the osteopetrotic (Op) mouse, which has a mutation in the macrophage colony stimulating factor (Csf1) gene. However, it is unknown whether monocytes/macrophages are implicated in adverse vascular effects of ET-1. We hypothesized that reduction in monocytes/macrophages would blunt ET-1-induced vascular injury. We performed a study on 4- to 6-month-old male mice with endothelium-specific ET-1 overexpression (eET-1), reduction in CSF1 (Csf1(Op/+)), or both (eET-1/Csf1(Op/+)), and their wild-type littermate control mice. There was no difference in systolic blood pressure between groups. Endothelial function and vascular structure were determined on a pressurized myograph. Endothelium-dependent relaxation in response to acetylcholine was similar in eET-1 and eET-1/Csf1(Op/+) mice. Media:lumen ratio and media cross-sectional area were ≈1.5-fold greater in eET-1 than in wild-type mice ($P<0.05$), which was not observed in mice deficient in CSF1. ET-1-induced oxidative stress measured by dihydroethidium staining ($P<0.05$) and NADPH oxidase activity assessed with lucigenin chemiluminescence ($P<0.05$) were blunted by CSF1 deficiency. ET-1 caused a 2.5-fold increase in monocyte/macrophage infiltration compared with wild-type mice ($P<0.001$), which was blunted in the mice deficient in CSF1. Reduction of monocyte/macrophage-dependent inflammation in mice overexpressing ET-1 in endothelium results in reduced vascular remodeling and oxidative stress, providing evidence for a role of monocytes/macrophages and innate immunity in ET-1-induced vascular injury.

KEYWORDS:

CSF1; innate immunity; macrophage colony stimulating factor; monocytes; osteopetrosis mutation; oxidative stress; vascular remodeling